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Incidence, risk factors, and prognosis of stroke in people with type 1 diabetes

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ACADEMIC DISSERTATION

To be presented, with the permission of the Medical Faculty of the University of Helsinki,
for public examination in Auditorium 2, Biomedicum Helsinki, Haartmaninkatu 8
on March 26th, 2021, at 12 noon.

Helsinki 2021

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The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

ISBN 978-951-51-7123-8 (paperback)
ISBN 978-951-51-7124-5 (PDF)
http://ethesis.helsinki.fi

Unigrafia Oy
Helsinki 2021

To Henrik, Lucas and Alva

"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less"

Marie Curie

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Hägg S, Thorn LM, Putaala J, Liebkind R, Harjutsalo V, Forsblom CM, Gordin D, Tatlisumak T, Groop PH; FinnDiane Study Group. Incidence of stroke according to presence of diabetic nephropathy and severe diabetic retinopathy in patients with type 1 diabetes. *Diabetes Care* 2013;36:4140-4146

II Hägg S, Thorn LM, Forsblom CM, Gordin D, Saraheimo M, Tolonen N, Wadén J, Liebkind R, Putaala J, Tatlisumak T, Groop PH; FinnDiane Study Group. Different risk factor profiles for ischemic and hemorrhagic stroke in type 1 diabetes. *Stroke* 2014;45:2558-2562

III Hägg-Holmberg S, Dahlström EH, Forsblom CM, Harjutsalo V, Liebkind R, Putaala J, Tatlisumak T, Groop PH, Thorn LM; FinnDiane Study Group. The role of blood pressure in risk of ischemic and hemorrhagic stroke in type 1 diabetes. *Cardiovascular Diabetology* 2019;18:88

IV Hägg-Holmberg S, Thorn LM, Forsblom CM, Gordin D, Elonen N, Harjutsalo V, Liebkind R, Putaala J, Tatlisumak T, Groop PH; FinnDiane Study Group. Prognosis and its predictors after incident stroke in patients with type 1 diabetes. *Diabetes Care* 2017;40:1394-1400

These publications are referred to in the text by their Roman numerals and have been reprinted with the kind permission of their copyright holders.

ABBREVIATIONS

24-h K	24-hour urinary potassium excretion
24-h Na	24-hour urinary sodium excretion
AHT	Antihypertensive treatment
BMI	Body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CT	Computed tomography
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
DN	Diabetic nephropathy
eGDR	Estimated glucose disposal rate
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FinnDiane	Finnish Diabetic Nephropathy
HbA_{1c}	Glycosylated hemoglobin A_{1c}
HDL	High-density lipoprotein
Hilmo	National Care Register for Health Care
Hp	Haptoglobin
HR	Hazard ratio
hs-C-reactive protein	High-sensitivity C-reactive protein
ICD	International Classification of Diseases
ICH	Intracerebral hemorrhage
JS	Joint Statement criteria
KDIGO	Kidney Disease: Improving Global Outcomes
LACI	Lacunar infarction
LDL	Low-density lipoprotein
MRI	Magnetic resonance imaging
NCEP	National Cholesterol Education Program Adult Treatment Panel III criteria
Na/K ratio	Sodium/potassium ratio
PACI	Partial anterior circulation infarct
Pittsburgh EDC	Pittsburgh Epidemiology of Diabetes Complications
POCI	Posterior circulation infarct
SAH	Subarachnoid hemorrhage
SDR	Severe diabetic retinopathy
TACI	Total anterior circulation infarct
TIA	Transient ischemic attack
UAER	Urinary albumin excretion rate
WHR	Waist-to-hip ratio

ABSTRACT

Background. Individuals with type 1 diabetes have a 5- to 20-times higher risk of suffering a stroke when compared with both individuals who have type 2 diabetes and the general population. Such individuals also have a worse prognosis after suffering a stroke. Yet, only a few prior studies have investigated the incidence and risk factors associated with stroke and its subtypes in individuals with type 1 diabetes. Furthermore, the predictors of survival following a stroke remain unclear.

Aim. This study sought to examine the incidence and risk factors associated with stroke in individuals with type 1 diabetes. It also sought to elucidate the prognosis and related predictors following an incident stroke in individuals with type 1 diabetes.

Participants and methods. This study was conducted as part of the nationwide, multicenter FinnDiane Study, which aims to discover the genetic, environmental, and clinical risk factors associated with micro- and macrovascular complications in individuals with type 1 diabetes. The population for Studies I, II, and IV comprised 4,083 participants with type 1 diabetes, of whom 149 had suffered an incident stroke. The population for Study III comprised 4,105 participants with type 1 diabetes, of whom 202 had suffered an incident stroke. All four studies were observational follow-up studies. All the included participants were examined according to the same examination protocol. Individuals with type 1 diabetes who had suffered a stroke were identified through the FinnDiane Study questionnaires, death certificates, and the National Care Register for Health Care, as based on the tenth revision of the International Classification of Diseases (codes I60–I64). The participants' strokes were classified into different subtypes based on their medical files and brain images.

Results. The incidence of stroke and its subtypes (i.e., ischemic stroke, lacunar infarction, and hemorrhagic stroke) increased with the presence of both severe diabetic retinopathy and advancing diabetic nephropathy. A long duration of diabetes, poor glycemic control, high systolic blood pressure, a history of smoking, and lower insulin sensitivity were all found to be independent risk factors for ischemic stroke, while high systolic blood pressure and a lower body mass index were found to increase the risk of hemorrhagic stroke, along with severe diabetic retinopathy and diabetic nephropathy. The risk factors associated with lacunar infarctions were determined to be similar to those associated with ischemic stroke.

All the different blood pressure variables (i.e., systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure) were found to be associated with an increased risk of stroke in individuals with type 1 diabetes. The risk of stroke increased in a linear fashion with increasing blood pressure, while no effect on the risk of stroke was identified in relation to urinary sodium and potassium excretion. The overall likelihood of survival following an incident stroke was found to be poor, with around 53% of participants having died during the mean follow-up period of 3.4 years. Ischemic stroke was observed to be associated with a better prognosis than hemorrhagic stroke, especially during the first year following the stroke. The predictors of a worse outcome were found to be a stroke of hemorrhagic origin, worsening kidney function, and the presence of end-stage renal disease.

Conclusions. Individuals with type 1 diabetes who suffer a stroke are generally of poorer health and have more diabetic complications, higher blood pressure, and worse glycemic control than individuals with type 1 diabetes who do not suffer a stroke. Both elevated systolic blood pressure and diabetic kidney disease represent important risk factors with regard to the development of stroke. The prognosis following a stroke is poor in individuals with type 1 diabetes, and the presence of diabetic kidney disease has a substantially negative effect on their prognosis. In terms of the prevention and treatment of stroke, it is important to identify these high-risk individuals. This could be achieved through regular measurements of the blood pressure and blood glucose levels of individuals with type 1 diabetes, in addition to screening for albuminuria.

ABSTRAKT (ABSTRACT IN SWEDISH)

Bakgrund. Personer med typ 1-diabetes har en 5–20-faldig risk för stroke jämfört med personer med typ 2-diabetes, samt personer utan diabetes. Prognosen efter en stroke är också sämre vid typ 1-diabetes. Trots detta finns det få studier som utreder incidens och riskfaktorer för stroke vid typ 1-diabetes. Det är också oklart vilka faktorer som påverkar prognosen efter en stroke vid typ 1-diabetes.

Studiens målsättningar. Målsättningen med denna avhandling var att utreda incidensen samt riskfaktorerna för stroke hos personer med typ 1-diabetes. Dessutom ville vi utreda vad prognosen är efter en stroke, samt vilka faktorer som påverkar den här prognosen.

Patienter och metoder. Den här avhandlingen är en del av den nationella multicenterstudien FinnDiane, vars mål är att utreda genetiska, miljöbetingade och kliniska riskfaktorer för mikro- och makrovaskulära komplikationer vid typ 1-diabetes. Populationen i studierna I, II och IV består av 4083 deltagare med typ 1-diabetes. Av dessa insjuknade 149 personer i en stroke för första gången under uppföljningstiden. Populationen i studie III består av 4105 deltagare med typ 1-diabetes, varav 202 insjuknade i en stroke för första gången under uppföljningstiden. Alla studierna är empiriska uppföljningsstudier. Alla inkluderade deltagare genomgick samma undersökningsprotokoll via FinnDiane-studien. Stroke identifierades från FinnDiane-studiens frågeformulär, dödscertifikat, samt det nationella vårdanmälningssystemet, baserat på den tionde upplagan av den Internationella statistiska klassifikationen av sjukdomar och relaterade hälsoproblem (ICD-koderna I60-I64). Stroke klassificerades i undergrupper på basen av patientjournaler samt radiologiska bilder på hjärnan.

Resultat. Incidensen för stroke samt undertyperna hjärninfarkt, lakunär infarkt och hjärnblödning var högre vid allvarlig diabetesretinopati och diabetesnefropati. Incidensen ökade i takt med att diabetesnefropatin framskred. Lång diabetesduration, dålig blodsockerbalans, högt systoliskt blodtryck, rökningsbakgrund och låg insulinkänslighet var alla självständiga riskfaktorer för hjärninfarkt, medan högt systoliskt blodtryck och lågt kroppsmasseindex, tillsammans med diabetesnefropati och diabetesretinopati, självständigt ökade risken för hjärnblödning. De självständiga riskfaktorerna för lakunär infarkt var de samma som för hjärninfarkt. De olika blodtryckskomponenterna, dvs systoliskt blodtryck, diastoliskt blodtryck, pulstryck samt medelartärtryck var alla associerade med en förhöjd risk för stroke vid typ 1-diabetes. Risken för stroke ökade lineärt i takt med att blodtrycket steg.

Utsöndringen av natrium och kalium i urinen påverkade inte risken för stroke. Prognosen efter en stroke var dålig, 53 % av deltagarna dog under uppföljningstiden på 3,4 år. Hjärninfarkt hade en bättre prognos än hjärnblödning, speciellt under det första året efter stroken. Hjärnblödning och försämrad njurfunktion, speciellt njursjukdom i slutskedet, var riskfaktorer för en sämre prognos.

Slutsatser. Personer med typ 1-diabetes som insjuknar i en stroke är i allmänhet sjuka, de har mer diabetiska komplikationer och högre blodtryck, samt sämre blodsockerbalans än de personer med typ 1-diabetes som inte får en stroke. Högt systoliskt blodtryck samt diabetisk njursjukdom är viktiga riskfaktorer för uppkomsten av stroke. Prognosen efter en stroke är också dålig, och förekomsten av diabetisk njursjukdom påverkar prognosen till en stor del. För att förebygga och inleda vård av stroke vid typ 1-diabetes är det därmed viktigt att identifiera dessa hög-riskpersoner i tid. Regelbunden uppföljning av blodtrycket och blodsockret, samt sållning för albuminuri är de viktigaste redskapen för att identifiera dessa personer.

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Tausta. Tyypin 1 diabetesta sairastavilla henkilöillä on 5–20-kertainen riski sairastua aivohalvaukseen verrattuna tyypin 2 diabetesta sairastaviin henkilöihin ja ei-diabeetikoihin. Heillä on myös huonompi ennuste sairastetun aivohalvauksen jälkeen. Tutkimuksia aivohalvauksen esiintyvyydestä ja riskitekijöistä tyypin 1 diabeteksessa on tästä huolimatta vähän. Lisäksi aivohalvauksen jälkeisen ennusteeseen vaikuttavia tekijöitä tyypin 1 diabetesta sairastavilla henkilöillä tunneta.

Tavoitteet. Tämän väitöskirjan tavoitteena oli selvittää aivohalvauksen esiintyvyyttä ja riskitekijöitä tyypin 1 diabetesta sairastavilla henkilöillä, sekä selventää mikä on aivohalvauksen jälkeinen ennuste ja mitkä tekijät tähän vaikuttavat.

Aineisto ja menetelmät. Tämä väitöskirja on osa FinnDiane-tutkimusta, joka on kansallinen monikeskustutkimus, jonka tavoitteena on selvittää geneettisiä, kliinisiä ja ympäristöllisiä riskiekijöitä mikro- ja makrovaskulaarisiin liitännäissairauksiin tyypin 1 diabeteksessa. Osatutkimusten I, II ja IV:n potilasaineisto koostuu 4083 tyypin 1 diabetesta sairastavasta henkilöstä, joista 149 sairastui ensimmäiseen aivohalvaukseen seuranta-aikana. Osatutkimus III:n potilasaineisto koostuu 4105 tyypin 1 diabetesta sairastavasta henkilöstä, joista 202 sairastui ensimmäiseen aivohalvaukseen seuranta-aikana. Kaikki osatutkimukset ovat empiirisiä seurantatutkimuksia. Kaikki tutkimukseen osallistujat tutkittiin samalla FinnDiane-tutkimusprotokollalla. Aivohalvaukset tunnistettiin FinnDiane-tutkimuksen kyselylomakkeesta, kuolintodistuksista sekä kansallisesta Hoitoilmoitusrekisteristä kansainvälisen tautiluokitusten perusteella (ICD-koodit I60-I64). Aivohalvaukset luokiteltiin alaluokkiin sairaskertomusten ja aivojen radiologisten kuvantamislöydösten perusteella.

Tulokset. Aivohalvauksen sekä alaluokkien (aivoinfarktit, lakunaariset infarktit ja aivoverenvuodot) esiintyvyys oli korkea henkilöillä, joilla oli samanaikaisesti diabeettinen retinopatia ja diabeteksen munuaistauti. Esiintyvyys oli sitä korkeampi, mitä vaikeampi diabeteksen munuaistauti oli. Pitkä diabeteksen kesto, huono verensokeritasapaino, korkea systolinen verenpaine, tupakointitausta ja huonompi insuliiniherkkyys olivat aivoinfarktin itsenäisiä riskitekijöitä, kun taas korkea systolinen verenpaine ja matala painoindeksi olivat diabeettisen retinopatian ja diabeettisen munuaistaudin lisäksi aivoverenvuodon itsenäisiä riskitekijöitä. Lakunaarisen infarktin riskitekijät olivat samat kuin aivoinfarktin riskitekijät. Kaikki erilliset verenpainekomponentit, eli systolinen verenpaine, diastolinen verenpaine, keskiverenpaine ja pulssipaine lisäsivät riskiä sairastua aivohalvaukseen

tyypin 1 diabeteksessa. Aivohalvauksen riski nousi lineaarisesti verenpaineen nousun yhteydessä. Virtsaan erittyvä natrium ja kalium eivät vaikuttaneet aivohalvauksen riskiin. Ennuste aivohalvauksen jälkeen oli heikko, 53 % osallistujista kuoli 3,4 vuoden keskimääräisen seuranta-ajan aikana. Aivoinfarktiin sairastuneilla oli parempi ennuste verrattuna aivoverenvuotoon sairastuneilla, mikä näkyi varsinkin ensimmäisen vuoden aikana aivohalvauksen jälkeen. Ennustetta huonontavat tekijät olivat aivoverenvuoto, heikentynyt munuaisten toiminta ja varsinkin loppuvaiheen diabeteksen munuaistauti.

Päätelmät. Aivohalvaukseen sairastuneet tyypin 1 diabetesta sairastavat henkilöt ovat yleisesti sairaampia kuin tyypin 1 diabetesta sairastavat henkilöt ilman aivohalvausta, ja heillä on enemmän diabeettisia komplikaatioita, korkeampi verenpaine sekä huonompi verensokeritasapaino. Korkea systolinen verenpaine sekä diabeteksen munuaistauti ovat tärkeitä aivohalvauksen riskitekijöitä. Ennuste sairastetun aivohalvauksen jälkeen on myös heikko, ja diabeteksen munuaistauti vaikuttaa ennusteeseen suuresti. Aivohalvauksen ennaltaehkäisyn ja hoidon kannalta on erittäin tärkeää tunnistaa nämä korkean riskin henkilöt. Säännöllinen verenpaineen ja verensokerin seuranta sekä albuminurian seulonta virtsasta ovat tärkeimmät välineet näiden henkilöiden tunnistamiseksi.

1 INTRODUCTION

Diabetes affected around 463 million people aged 20–79 years worldwide in 2019, and unfortunately, its incidence is still increasing. Indeed, it has been estimated that by 2045, as many as 700 million people will suffer from this chronic disease. (1) Around 10% of individuals with diabetes suffer from what was formally known as childhood-onset diabetes, which is now referred to as type 1 diabetes. This means that there are approximately 46 million people with type 1 diabetes worldwide (1,2). Finland has one of the highest rates of type 1 diabetes in the world, with almost 53,000 people having been diagnosed with type 1 diabetes by the end of 2017 (3). Diabetes not only affects individuals' blood glucose levels, as it also results in other metabolic disturbances, such as disturbances in blood pressure and lipid regulation, which can lead to chronic micro- and macrovascular complications (4). Diabetic nephropathy and diabetic retinopathy, along with diabetic neuropathy, represent the microvascular complications associated with diabetes. These chronic complications can have devastating consequences, including blindness and the need for dialysis treatment, kidney transplantations, and lower extremity amputations. (5) Furthermore, the consequences of the macrovascular complications of diabetes and the resultant cardiovascular disease, which mostly manifests as ischemic heart disease and stroke (5), are similarly gruesome, leading to impaired quality of life and excessive mortality in those affected (6,7). After ischemic heart disease, stroke represents the second leading cause of death worldwide (8). In 2016, almost 14 million people worldwide suffered a stroke (9). While the mortality rate associated with stroke has decreased, the number of survivors living with disabilities that affect their everyday life has increased. Stroke is, therefore, the disease that most commonly results in disability among sufferers (10). Stroke is usually subclassified into ischemic stroke, which is caused by the occlusion of the cerebral arteries, and hemorrhagic stroke, which is caused by the rupture of the cerebral blood vessels or aneurysms in the brain, although both lead to the obstruction of the cerebral blood flow and damage to the cerebral tissue (11). Ischemic stroke can be further subclassified into non-lacunar infarction (i.e., stroke due to the occlusion of the large arteries) and lacunar infarction (i.e., the occlusion of a single perforating artery, which causes less severe damage when compared with non-lacunar infarction) (12). The division of stroke into strokes of ischemic or hemorrhagic origin is important because there are differences in terms of the prevention and management of these two major subtypes (11).

Diabetes is considered to be one of the strongest risk factors for stroke (13,14). Having type 2 diabetes increases the risk of stroke by up to five times (15), while

the risk can be up to 20 times higher in individuals with type 1 diabetes (16), when compared with the general population. Yet, despite the high risk of stroke in individuals with diabetes, information on stroke in individuals with type 1 diabetes remains scarce. Only a few studies have investigated the incidence of stroke in those with type 1 diabetes, and due to the small number of strokes in those studies, the incidence of the stroke subtypes (ischemic stroke, hemorrhagic stroke, and lacunar infarction) could not be elucidated (13,17). The way in which diabetes affects the risk of lacunar infarction is unclear; however, there seems to be a link between chronic kidney disease, retinal microvascular changes, and lacunar infarctions even without the presence of diabetes (18,19). Given that cerebral small-vessel disease is a common finding in individuals with diabetes (20), it is important to study the effect of diabetic microvascular complications on the risk of stroke, especially lacunar infarction, in those with type 1 diabetes.

Aside from diabetes, the other well-known risk factors for stroke in the general population include an older age, hypertension, smoking, and atrial fibrillation (21-23). In individuals with type 2 diabetes, similar risk factors have been observed (24). Additionally, the metabolic syndrome and its components have been found to increase the risk of stroke, especially in individuals with type 2 diabetes (25). In those with type 1 diabetes, the risk factors for stroke appear to differ from the risk factors mentioned above. In fact, in individuals with type 1 diabetes, a longer duration of diabetes, elevated systolic blood pressure, higher glycosylated hemoglobin A_{1c} (HbA_{1c}), and overt diabetic nephropathy have been identified as risk factors for any type of stroke (17). Diabetic nephropathy, which is a form of chronic kidney disease, occurs in 20–40% of all individuals with diabetes (26). It remains unclear how mildly decreased kidney function or moderately increased albuminuria affect the risk of stroke and its subtypes in individuals with type 1 diabetes. Moreover, the effects of diabetic retinopathy and other potential risk factors on stroke and its subtypes also remain unclear in those with type 1 diabetes.

Elevated blood pressure is one of the strongest risk factors for stroke among both the general population and those with diabetes (21,24). The blood pressure can be deconstructed into different components, of which the systolic blood pressure represents the maximum pressure the blood exerts against the artery walls when the heart beats, while the diastolic blood pressure represents the minimum pressure. With age, the systolic blood pressure increases in a linear fashion, while the diastolic blood pressure starts to decrease, mainly due to reduced vascular compliance. The pulse pressure represents the difference between the systolic and diastolic blood pressures. This component naturally increases with age due to the described changes in the systolic and diastolic blood pressures, and it can be used as a measurement of arterial stiffness. (27) The pulse pressure is a predictor of stroke in the general population (28), although the effect that it and the other blood pressure components have on the risk of stroke in individuals with type 1

diabetes has not yet been studied. The risk of stroke increases in a linear fashion with increasing blood pressure in the general population (21). In those with type 2 diabetes, however, lower blood pressure levels also seem to increase the risk of stroke, especially in individuals under the age of 60 (29). Determining whether this is also the case in individuals with type 1 diabetes requires further studies.

The mortality rate associated with stroke is high, with more than 25% of those who experience an incident stroke dying within a year (30). Age, hemorrhagic stroke, the male sex, and diabetes all predict a higher mortality rate in the general population (31,32). In addition, proteinuria and diabetic nephropathy strongly predict severe disability and a high mortality rate in individuals with type 2 diabetes (33,34). In those with type 1 diabetes, the prognosis after an incident stroke also appears to be poor. In the only prior study concerning this issue, more than half of the rather young participants with the mean age of 40.2 years died within five years after experiencing a stroke (17). Neither the impact of the stroke subtypes nor the predictors of the participants' prognosis were elucidated in that study, meaning that further research is required.

2 REVIEW OF THE LITERATURE

2.1 Diabetes mellitus

Diabetes mellitus is a chronic systemic disease characterized by elevated blood glucose levels (or hyperglycemia). This hyperglycemic condition may cause fatigue, excess urine production, systematic organ damage, and eventually, death. For centuries, no treatment was available for diabetes, and it was not until the discovery of insulin by Paulescu in 1921, as well as the subsequent extraction and administration of this hormone by Banting and Best in 1922, that the treatment of diabetes was revolutionized. (4)

2.1.1 Classification of diabetes

Type 1 and type 2 diabetes. Diabetes is defined as a fasting plasma glucose of ≥ 7.0 mmol/l, a two-hour plasma glucose of ≥ 11.1 mmol/l during an oral glucose tolerance test, an HbA_{1c} of ≥ 48 mmol/mol, and/or a random plasma glucose of ≥ 11.1 mmol/l that causes symptoms (35,36). Diabetes not only causes chronic hyperglycemia and a carbohydrate imbalance, but also results in a disturbance in lipid and protein metabolism. Diabetes is caused by either insulin deficiency or insulin resistance, or sometimes, a combination of the two. The two major types of diabetes are type 1, which was formerly known as childhood-onset diabetes, and type 2, which was formerly known as adult-onset diabetes. In the case of type 1 diabetes, an autoimmune-associated process leads to the destruction of the insulin-producing β cells in the islets of Langerhans within the pancreas, thereby leading to total insulin deficiency in the individual. The afflicted individual is thus dependent on exogenous insulin for survival, and treatment with insulin is usually initiated immediately following diagnosis. Several genetic and environmental factors have been found to be associated with the development of type 1 diabetes, which is also the case when it comes to type 2 diabetes. (37)

Type 2 diabetes is characterized by a relative insulin deficiency caused by β-cell dysfunction as well as insulin resistance within the target organs. Type 2 diabetes is more commonly associated with obesity, a sedentary lifestyle, and an older age than type 1 diabetes; however, the prevalence of type 2 diabetes is increasing in young adults and children. Type 2 diabetes is usually treated with one or more glucose-lowering agents, and in many cases, with insulin as well. (37) Recently, a new means of classifying the different types of diabetes has been proposed, which highlights the fact that diabetes is a heterogenous disease with different phenotypes and different prognoses. This classification is based

on insulin deficiency and resistance, the presence of glutamic acid decarboxylase autoantibodies, metabolic derangements, and the age at onset. The intention behind this new classification is to allow for the tailoring of treatment to the specific needs of the individuals within each group. (38)

2.1.2 Epidemiology of type 1 diabetes

There are currently approximately 460 million people with diabetes worldwide (1). Type 2 diabetes is the most common type, accounting for 85–90% of all cases, while approximately 10% of cases involve type 1 diabetes (1,2). In light of this, approximately 46 million people worldwide suffer from type 1 diabetes, making it one of the most common chronic autoimmune diseases in the world. Finland has the highest incidence of type 1 diabetes worldwide (40.9/100,000 per year in individuals under the age of 15), followed by Sardinia (37.8/100,000 per year). The lowest incidence is found in China and Venezuela, which both have an incidence of 0.1/100,000 per year. In contrast to other autoimmune diseases, type 1 diabetes is more common in men. (39)

The incidence of type 1 diabetes worldwide increased rapidly during the 20th century, reaching a plateau in the 1980s. After that, the incidence continued to rise, especially in young children under the age of 10. (40) Since the beginning of the 21st century, the incidence of type 1 diabetes in Finland has decreased in children under the age of five, while the incidence has remained the same in older children (41). The specific reasons for the increasing incidence are not known, although several theories exist. For instance, better health care and the adjustment of insulin treatment, as well as other factors that promote health, have led to increased survival. Furthermore, the increased overall survival rate has given rise to increased genetic survival and the passing on of genes related to diabetes. However, as more newly diagnosed cases of type 1 diabetes exhibit a reduced genetic predisposition toward the disease, other causes such as environmental factors must also lie behind the increase. (42)

2.1.3 Pathogenesis of type 1 diabetes

The pathogenesis of type 1 diabetes is not yet fully understood, although the interactions of genes, viral infections, and other environmental factors are all thought to play a role in the disease's development (37). The disease clusters within families (43). More specifically, if the mother has type 1 diabetes, the cumulative risk of the offspring having type 1 diabetes is 5%, while the risk is 8% if the father is affected (44). No single gene has been found to increase the risk of type 1 diabetes; however, different loci have been associated with the disease. One of the most well-known genes associated with type 1 diabetes is part of the human leukocyte

antigen complex. (37) Other genetic regions have also been identified, and most of them are connected to functions affecting the immune response system (45,46).

The exact mechanism behind the autoimmune destruction of the β-cells within the pancreas (i.e., insulitis) remains unknown, although autoantibodies seem to play a role in activating the autoimmune response. Moreover, the triggers behind the autoimmune response in genetically prone individuals remain unclear. (37) Bacterial and viral infections represent one of the most widely discussed environmental factors responsible for the activation of autoantibody development. In particular, Coxsackievirus B1 is believed to play a significant role in this (47). In accordance with this theory, a vaccine against this type of virus has been shown to be protective in relation to the development of type 1 diabetes in mice (48).

Other environmental risk factors that affect the development of type 1 diabetes include perinatal factors, for example, delivery via cesarean section (49), maternal obesity (50), and a high birth weight (51). The "hygiene hypothesis" suggests that the decrease in infectious diseases that results from better hygiene, health, and medical conditions during childhood leads to the inadequate development of the immune system and, therefore, the development of autoimmune diseases (52). This hypothesis is supported by the fact that the incidence of other autoimmune diseases, such as allergies and asthma, have increased as a result of the loss of protective environmental factors (53). Other environmental factors suggested to trigger the autoimmune reaction leading to type 1 diabetes include vitamin D deficiency (54,55) and changes in the gut microbiota (56).

2.2 Chronic diabetic complications

Type 1 diabetes, similar to the other forms of diabetes, may cause chronic complications. The hyperglycemic state and hypertension, among other things, affect the walls of the blood vessels, especially the small blood vessels in the retina, kidneys, and nerves (57). The complications caused by diabetes and hyperglycemia can be divided into micro- and macrovascular complications, depending on the sizes of the affected blood vessels. Macrovascular complications affect the larger blood vessels, resulting in coronary heart disease, stroke, and lower extremity arterial disease. Microvascular complications, as the name suggests, affect the smaller blood vessels, and they comprise diabetic nephropathy, retinopathy, and neuropathy. (5) Not only do these chronic diabetic complications result in a great burden on the health-care system (58), they also lead to excessive mortality (7,59) and impaired quality of life in individuals with diabetes (6).

2.2.1 Diabetic nephropathy

Terminology. The preferred terminology concerning the diabetic microvascular complication diabetic nephropathy has changed in recent years. According to Kidney Disease: Improving Global Outcomes (KDIGO), an international organization dedicated to developing evidence-based guidelines regarding kidney disease, this complication should now be referred to as diabetic kidney disease (60). However, at the time the studies included in this thesis were conducted, the preferred term was diabetic nephropathy, which is why diabetic kidney disease is referred to as diabetic nephropathy in the present thesis. The terminology for the different stages of diabetic nephropathy, that is, microalbuminuria, macroalbuminuria, and end-stage renal disease, has also changed. Indeed, microalbuminuria is today referred to as moderately increased albuminuria, or albuminuria category A2, while macroalbuminuria is referred to as severely increased albuminuria, or albuminuria category A3. Moreover, a normal albumin excretion rate is referred to as normal to mildly increased albuminuria, or albuminuria category A1. According to these new guidelines, the term end-stage renal disease should be referred to as kidney failure. (60) Due to the fact that the old terminology was the preferred approach at the time the studies included in this thesis were conducted, the terms microalbuminuria, macroalbuminuria, and end-stage renal disease will be used throughout.

Classification and pathophysiology. Diabetes is the most common cause of chronic kidney disease worldwide (61). Also known as diabetic nephropathy, this complication develops in 20–40% of all individuals with diabetes (26). In the case of diabetic nephropathy, the damaged kidneys lead to the loss of kidney function. The progression of diabetic nephropathy can eventually lead to complete kidney failure, leaving the individual in need of dialysis or a kidney transplant in order to survive. In diabetes, hyperglycemia and hypertension, among other complications, damage the small blood vessels of the kidneys, specifically the glomeruli, which represent the functional part of the kidneys. This leads to glomerular hyperfiltration, which is clinically indicated by protein, or albumin, leakage into the urine (or albuminuria). (62) Based on the amount of albumin in the urine, diabetic nephropathy can be divided into four stages: a normal urinary albumin excretion rate (UAER), microalbuminuria, macroalbuminuria, and end-stage renal disease (63). According to the KDIGO guidelines, the current corresponding terminology is normal to mildly increased albuminuria, moderately increased albuminuria, severely increased albuminuria, and kidney failure, respectively (60).

The development and progression of diabetic nephropathy usually takes decades. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study revealed that more than 50% of individuals with type 1 diabetes develop microalbuminuria

within 30 years of their diabetes diagnosis. Diabetic nephropathy progresses in many individuals, as determined in the same study. More specifically, 22% of those with type 1 diabetes died after 30 years of having diabetes due to the complications of end-stage renal disease. (64) Early intervention and treatment reduce the risk of developing microalbuminuria and macroalbuminuria, thereby also reducing the risk of end-stage renal disease (65). The incidence of diabetic nephropathy in individuals with type 1 diabetes has fortunately decreased over the last few decades due to improved treatment options and the early detection of albuminuria (66,67). Not all of those who develop albuminuria progress to a subsequent stage, and the regression of this complication is also possible. In a study conducted as part of the FinnDiane Study, 23% of those with both microalbuminuria and macroalbuminuria regressed to a lower category of albuminuria, while the risk of developing cardiovascular complications in these individuals also diminished (68). In addition, not all diabetes-related kidney diseases are associated with albuminuria. For instance, in people with type 2 diabetes, non-albuminuric renal disease is prevalent, being observed in 39–55% of all those with chronic kidney disease (69,70), while in people with type 1 diabetes it is observed in only 16% (71).

Screening and diagnosis. The diagnosis of diabetic nephropathy is based on the amount of albumin in the urine. Screening for albuminuria is usually performed through the annual measurement of the urinary albumin-to-creatinine ratio from a random spot urine collection. Screening for albuminuria should be commenced ≥ 5 years after the diagnosis of diabetes in those with type 1 diabetes, and immediately at the time of diagnosis in those with type 2 diabetes. A normal urinary albumin-to-creatinine ratio is defined as < 30 mg/g, while a high urinary albumin excretion is defined as ≥ 30 mg/g. For a diagnosis of albuminuria, an increased urinary albumin-to-creatinine ratio should be seen in two out of three urine collections during a three- to six-month period. This is mainly due to confounding factors, such as infections, fever, strenuous exercise, congestive heart failure, and menstruation, which may cause transient albuminuria without the presence of diabetic nephropathy. Timed or 24-hour urine collections for the detection of albumin are also possible, although they require more work. (72) The first sign of diabetic nephropathy is microalbuminuria. In people with microalbuminuria, which is now referred to as moderately increased albuminuria, the UAER is ≥ 30 and < 300 mg/24h, or ≥ 20 and < 200 μg/min. No other symptoms are usually present at this time. When the UAER exceeds ≥ 300 mg/24h or ≥ 200 μg/min, the individual is said to have macroalbuminuria, or severely increased albuminuria. (60,73) This stage is characterized by proteinuria, high blood pressure (74), and an eventual decline in kidney function (75). With the progression of macroalbuminuria, end-stage renal disease, or kidney failure, will eventually develop. End-stage renal disease is defined as uremia and non-

existent kidney function, and it leaves the affected individual dependent on dialysis treatment or renal replacement therapy. (75) As previously mentioned, regression between the different stages is also possible (68,76).

Another way to describe and grade diabetic kidney disease involves kidney function. Kidney function is usually estimated using formulae developed specifically for this purpose (77-79). The formula that is most commonly used today for the estimation of the glomerular filtration rate (eGFR) is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which includes the individual's serum creatinine level, age, sex, and ethnicity (80). This method is considered to be more accurate than the other available methods because it estimates the glomerular filtration rate rather than the rate of creatinine clearance, which overestimates the glomerular filtration rate. The eGFR estimates the filtration capacity of the kidney, and the lower the value, the poorer the function. With this method, kidney function is classified into the five stages of chronic kidney disease (Table 1). Today, the stages of chronic kidney disease should not only be defined according to the eGFR, but also according to the albuminuria category (60), as shown in Table 1.

TABLE 1. Stages of chronic kidney disease according to the eGFR stage and level of albuminuria, adapted from the Kidney Disease: Improving Global Outcomes and American Diabetes Association guidelines (60,72), and including terminology used in this thesis.

CKD risk categories according to the CKD stage and albuminuria			Albuminuria		
			Normal UAER	Micro-albuminuria	Macro-albuminuria
			Normal to mildly increased	Moderately increased	Severely increased
CKD Stage		eGFR (mL/min/1.73 m^2)	< 30 mg	≥ 30 and < 300 mg	≥ 300 mg
Stage 1	Normal or high	≥ 90			
Stage 2	Mildly decreased	60–89			
Stage 3a	Mildly to moderately decreased	45–59			
Stage 3b	Moderately to mildly decreased	30–44			
Stage 4	Severely decreased	15–29			
Stage 5	Kidney failure	< 15			

The white color depicts a low risk of CKD progression, the light grey color a moderately increased risk, the medium grey color a high risk, and the dark grey color a very high risk. eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease, UAER = urinary albumin excretion rate.

Risk factors. Elevated blood glucose and high blood pressure, which are both common in individuals with type 1 diabetes, are well-known risk factors for the development of diabetic nephropathy (81,82). In addition, an older age (83) and a longer diabetes duration (84) also increase this risk. Smoking is an independent risk factor for the development of diabetic nephropathy (85), and it both accelerates the loss of renal function and increases mortality if end-stage renal disease develops (86). Pre-eclampsia is also associated with an increased risk of diabetic nephropathy in those with type 1 diabetes (87). When it comes to dyslipidemia, both a higher total cholesterol level and a lower high-density lipoprotein (HDL)-cholesterol level increase the risk of renal insufficiency in individuals with type 1 diabetes (82). Obesity is also associated with an increased risk of the development of diabetic nephropathy (84,88). Gender appears to play a role, with the male sex being found to increase the risk of the progression of diabetic nephropathy (83). Furthermore, there is evidence of a genetic susceptibility to developing diabetic nephropathy (89). In those with type 1 diabetes, the diabetic micro- and macrovascular complications cluster within individuals, and the presence of diabetic retinopathy generally precedes the development of diabetic nephropathy (90).

Treatment. When it comes to managing diabetic nephropathy, annual screening for albuminuria is highly important. If, or when, microalbuminuria and diabetic nephropathy develop, the focus should be on treating the risk factors mentioned above. Intensive treatment and lowering both the blood glucose concentration and blood pressure should be the first interventions applied. (72) A stricter regimen of glycemic control should reduce the risk of developing both micro- and macroalbuminuria (91). High systolic and diastolic blood pressures accelerate the development of diabetic nephropathy, and aggressive blood pressure treatment leads to the recovery of the kidneys, diminishes the need for dialysis treatment or kidney transplantation, and reduces the mortality rate linked to renal failure (92). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have been shown to not only protect the kidneys and reduce the risk of the progression of diabetic nephropathy, but also to lower the cardiovascular risk associated with this complication, leading to them being the agents of choice when treating blood pressure in individuals with type 1 diabetes (93,94). However, if neither hypertension nor albuminuria are present, these agents will not prevent the development of diabetic nephropathy (95). The blood pressure target in individuals without albuminuria is < 140/90 mmHg, while in those who have developed microalbuminuria, the target is < 130/80 mmHg (96).

If end-stage renal disease develops, the kidneys are no longer able to filtrate urine, which leaves the individual in need of dialysis treatment or transplantation. This may occur in as many as 7% of individuals within 30 years of the diagnosis of

type 1 diabetes in Finland (66). Dialysis treatment limits the life of the individual, and both cardiovascular morbidity (97) and all-cause mortality (59) are greatly increased in cases of end-stage renal disease. For those who are eligible, renal transplantation leads to improved survival when compared with dialysis (98). In individuals with type 1 diabetes, simultaneous pancreas-kidney transplantation may be possible, resulting in the individual having restored kidney function and normal insulin production. Furthermore, survival after pancreas-kidney transplantation is substantially better than survival after kidney transplantation alone. (99)

2.2.2 Diabetic retinopathy

Classification and pathophysiology. In addition to being the most common microvascular complication of diabetes, diabetic retinopathy is the leading cause of blindness among adults in developed countries (100). Diabetic retinopathy is classified into the different stages of non-proliferative and proliferative retinopathy, with the proliferative form being the sight-threatening stage that requires treatment (101). Another form of diabetic retinopathy is macular edema, or diabetic maculopathy, which is caused by the thickening of the retina in the macular region. This can be present in both non-proliferative and proliferative retinopathy, and it represents a major threat to the individual's vision. (102) The age-standardized prevalence of any type of diabetic retinopathy is 25% in those with type 2 diabetes, while in those with type 1 diabetes, the prevalence is as high as 77%. For proliferative diabetic retinopathy, the corresponding percentages are 3% and 33%, respectively. (103) Of all the individuals with type 1 diabetes who develop diabetic retinopathy, 5–10% will lose their vision (104).

The first sign of diabetic retinopathy is the swelling of the small blood vessels in the retina, or microaneurysms. As the complication progresses, intraretinal hemorrhages and cotton wool spots appear, while the blood vessels that nourish the retina may lose the ability to transport blood. In proliferative diabetic retinopathy, ischemia-induced neovascularization develops in the retina. These new blood vessels are fragile, and they have a tendency to bleed. Vision loss occurs partly due to this. Furthermore, the development of the new blood vessels leads to the accompanying fibrous tissue distorting the retina. Moreover, the individual's central vision can be impaired by the macular edema caused by increased vascular permeability and the loss of capillary perfusion. (101,105)

Risk factors. Diabetic retinopathy is closely associated with the duration of diabetes. In a study by Yau *et al*, no risk of developing proliferative diabetic retinopathy was seen in those with type 1 diabetes during the first 10 years after the diagnosis of diabetes. However, if the duration was more than 10 years, the risk

increased almost seven-fold. (103) Next to the diabetes duration, poor glycemic control is a major risk factor for the development of diabetic retinopathy (106). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) showed that intensive treatment of the blood glucose decreased the risk of the progression of diabetic retinopathy by more than 70% (107). As in the case of diabetic nephropathy, hypertension increases the risk of diabetic retinopathy (108). In individuals with type 1 diabetes, lowering the blood pressure reduces the incidence (109) and progression of diabetic retinopathy (106). Although not as strong as the risk factors mentioned earlier, dyslipidemia also increases the risk of diabetic retinopathy (106). Smoking has been associated with diabetic retinopathy in a cross-sectional study (110); however, no such association has been found in prospective studies (106,111). Moreover, there seems to be a genetic predisposition toward diabetic retinopathy. As observed in the same study, the severity of diabetic retinopathy is closely associated with the severity of diabetic nephropathy. (112)

Screening, diagnosis, and treatment. Diabetic retinopathy is diagnosed by means of fundus photography or ophthalmoscopy. Screenings are performed regularly in individuals with diabetes in order to identify those who are at risk of developing sight-threatening changes (72). Through regular screenings, early detection, and the treatment of diabetic retinopathy, up to 98% of visual loss due to this complication can be prevented (113). Screenings in those with type 1 diabetes should be initiated within five years of onset, and if no signs of retinopathy are present, subsequent screenings should be performed every 1–2 years (72). Good glycemic control and the prevention of modifiable risk factors such as hypertension and dyslipidemia are key to the prevention and treatment of diabetic retinopathy (101,114). However, the overly swift lowering of the blood glucose concentrations in those who have already developed retinopathy may exacerbate the retinopathy itself (115). When proliferative diabetic retinopathy develops, retinal laser treatment is required to mitigate vision disturbances and prevent vision loss (116).

2.2.3 Diabetic neuropathy

As the most common of all the neuropathies worldwide, diabetic neuropathy develops in 50% of all individuals with any type of diabetes (117). The hyperglycemic state is thought to affect the nerves through causing demyelination and the degeneration of axons (118). Distal symmetric polyneuropathy is the most common form, and its symptoms include numbness, tingling and burning sensations, pain, weakness, loss of sensation, and loss of proprioception. The symptoms usually start distally in the lower extremities, before moving up to the

more proximal parts of the limbs, and eventually, also affecting the upper limbs. (117) The most important risk factors for diabetic neuropathy are the duration of diabetes and poor glycemic control (119).

Another form of diabetic neuropathy is autonomic neuropathy, which involves disturbances in the sympathetic and parasympathetic nervous systems (117). The symptoms can be divided into different organ functions, of which the most dangerous are the cardiovascular symptoms. These consist of resting tachycardia and orthostatic hypotension, in addition to silent myocardial infarction. (120) Other symptoms include gastroparesis, dysphagia, bladder dysfunction, sexual dysfunction, and difficulty recognizing hypoglycemia (117,120). The treatment of diabetic neuropathy focuses on improving glycemic control and pain management, and regular exercise is encouraged (117,118).

2.2.4 Cardiovascular disease and macrovascular complications

Epidemiology of cardiovascular disease and coronary heart disease. In comparison to microvascular disease, macrovascular disease has been studied to a lesser extent in those with type 1 diabetes, especially when it comes to the different hard cardiovascular endpoints. In most studies involving individuals with type 1 diabetes, the cardiovascular events (i.e., coronary heart disease, stroke, and lower extremity artery disease) are pooled into a common cardiovascular endpoint termed cardiovascular disease. This macrovascular complication contributes to almost 60% of all deaths in individuals with type 1 diabetes and with a diabetes duration of more than 20 years (121). Furthermore, even though the mortality rate and the incidence of end-stage renal disease have declined over recent decades in these individuals, the incidence of coronary heart disease has remained relatively high and unchanged (122). The risk of cardiovascular disease arises 10–15 years earlier in individuals with type 1 diabetes when compared with the general population. Men with type 1 diabetes have a four-fold higher risk of major cardiovascular disease, while the risk for women is almost eight-fold higher, when compared with the general population. (123) Soedemah-Muthu *et al* found that the highest relative risk of cardiovascular disease occurs in young women with type 1 diabetes under the age of 55 years when compared with women without diabetes of the same age, which demonstrates that the protective role of pre-menopause seen in the general population does not exist in those with type 1 diabetes (123,124).

Microvascular complications, cardiovascular disease, and all-cause mortality. When compared with individuals who have a normal UAER, microalbuminuria, the mildest form of diabetic nephropathy, doubles the risk of coronary heart disease and cardiovascular mortality in those with type 1 diabetes, although it must be recognized that confounding factors were not taken

into account in the relevant studies (123,125). Macroalbuminuria and diabetic nephropathy significantly affect the risk of hard cardiovascular events. In fact, individuals with diabetic nephropathy have a ten-fold higher risk of suffering from coronary heart disease and stroke when compared with those without nephropathy (126). Diabetic nephropathy also affects cardiovascular mortality. Borch-Johnson *et al* found an almost 40-fold higher risk of cardiovascular mortality in individuals with type 1 diabetes and diabetic nephropathy when compared with those without diabetic nephropathy. A particularly concerning fact is that the highest mortality rates were seen in young individuals between the ages of 26 and 45. (127) Groop *et al* found that the presence and the severity of chronic kidney disease increase the risk of all-cause mortality in individuals with type 1 diabetes (59). Similar results were found in the Pittsburgh EDC Study (128). As seen in these studies, the risk of all-cause mortality is three- to six-fold higher if microalbuminuria is present, nine- to 13-fold higher in the presence of macroalbuminuria, and 18- to 30-fold higher in the case of end-stage renal disease (59,128). Furthermore, the relationship between the eGFR and mortality shows a reverse J-shaped curve, whereby both a low eGFR under 60 ml/min/1.73m^2 and a high eGFR over 120 ml/min/1.73m^2 increase the mortality rate in those with type 1 diabetes (59).

Even though renal dysfunction is one of the strongest predictors of mortality in those with type 1 diabetes, a recent study found that individuals with a normal UAER and type 1 diabetes also face a higher risk of mortality when compared with the general population, mainly due to acute diabetes complications and ischemic heart disease (129). The other microvascular complications found in those with type 1 diabetes have not shown similarly strong relationships with cardiovascular disease. Diabetic retinopathy increases the risk of coronary heart disease when the individual's age and duration of diabetes are considered, but not if diabetic nephropathy is also present. The same is true for neuropathy. No independent associations between these two microvascular complications and coronary heart disease have been found, partly due to the strong relationship with diabetic nephropathy as well as other diabetes-related risk factors. (130)

Other risk factors for cardiovascular disease. As mentioned above, blood pressure can be divided into different variables, namely systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure. As first revealed in the Framingham Heart Study, the systolic blood pressure, among all the blood pressure components, has the strongest association with cardiovascular disease in the general population (131). Unsurprisingly, the systolic blood pressure is an independent risk factor for coronary heart disease in individuals with type 1 diabetes (130,132). With regard to the pulse pressure, this blood pressure component can be considered a measurement of arterial stiffness, and it usually rises with age (133). The pulse pressure is an independent risk factor for coronary

heart disease despite the elevated systolic blood pressure seen in the general population (134). In individuals with type 1 diabetes and renal disease, the pulse pressure is a predictor of incident cardiovascular events (135).

Elevated HbA_{1c} is an independent risk factor for both non-fatal and fatal cardiovascular events in those with type 1 diabetes (136,137). The risk of coronary heart disease increases in a linear fashion with higher blood glucose concentrations, and for every 1% unit increase in HbA_{1c}, the risk of coronary heart disease increases by 30% (136). In the well-known DCCT/EDIC studies, the intensive treatment of the glucose level during the DCCT in individuals with type 1 diabetes reduced the risk of any cardiovascular event by 42% and of fatal cardiovascular disease by 57%. Moreover, the effect persisted for years after the DCCT study ended. The observed risk reduction was mostly attributable to the improved glucose levels during the DCCT, and it was sustained for a prolonged time, although the difference in glucose control between the groups disappeared. (138)

In terms of the diabetes duration and the risk of coronary heart disease in individuals with type 1 diabetes, the results are somewhat contradictory. Some studies have found evidence that a diabetes duration of more than 20 years independently increases the risk of coronary heart disease (136,139), while other studies have found no such association (130).

In men with type 1 diabetes, a higher waist-to-hip ratio (WHR), which is indicative of obesity, increases the risk of coronary heart disease, although no similar association has been found in women (130). The metabolic syndrome increases the risk of cardiovascular disease in both the general population (140) and those with type 2 diabetes (141). In individuals with type 1 diabetes, the metabolic syndrome increases the risk of cardiovascular disease as well as the risk of both cardiovascular- and diabetes-related mortality (142). There is also evidence of an association between insulin resistance and the risk of coronary heart disease in those with type 1 diabetes (143).

While dyslipidemia is a strong risk factor for both cardiovascular disease and coronary heart disease in the general population (144) and those with type 2 diabetes (145), the results are not clear with regard to type 1 diabetes. Forrest *et al* found that low HDL-cholesterol levels independently increase the risk of coronary heart disease (132), while Soedemah-Muthu *et al* found no such association (130). Instead, higher fasting triglyceride levels were found to be modestly associated with an increased risk of coronary heart disease (130). In addition, higher HDL-cholesterol levels were seen to linearly decrease the risk of coronary heart disease in men with type 1 diabetes, while in women with type 1 diabetes, a J-shaped phenomenon is seen, meaning that the risk of coronary heart disease starts to increase again with an HDL-cholesterol level beneath 0.9 mmol/l (146).

2.3 Stroke

Stroke was defined by the World Health Organization in the 1970s as a sudden loss of neurological function due to a disruption to the blood circulation in the brain that persists for 24 hours or longer (147). In an updated definition, the term brain has been replaced with the term central nervous system. In addition to the brain, the updated definition includes the spinal cord and the retinal cells. Moreover, the focus is on tissue damage rather than the time limit of ≥ 24 hours for the symptoms to persist. (148) Stroke is the second leading cause of death worldwide after ischemic heart disease (8), and it is also one of the most common diseases causing disability worldwide (10). In 2016, almost 14 million people worldwide suffered an incident stroke (9).

2.3.1 Classification and pathophysiology of stroke

Ischemic stroke. Stroke is classified into two major subgroups, namely ischemic and hemorrhagic stroke (149). The majority, that is, approximately 75%, of all strokes are of ischemic origin. Ischemic stroke can be further classified into non-lacunar or lacunar stroke based on the mechanism leading to the stroke (i.e., the TOAST classification system) (150), the location of the stroke (151), or the phenotypic characteristics of the clinical stroke syndrome and the radiological features (12). The TOAST classification system divides ischemic stroke into five categories: large artery atherosclerosis due to embolus or thrombosis, cardioembolism, small-vessel occlusion (i.e., lacunar infarction), stroke of other determined cause, and stroke of undetermined cause (150). Bamford *et al* presented a classification system with four subgroups, namely total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI), and lacunar infarctions (LACI) (151). Pantoni *et al* classified ischemic stroke into two subgroups: non-lacunar (i.e., large-vessel stroke mainly due to either atherosclerosis of the carotid artery or cardioembolism) or lacunar (i.e., caused by the occlusion of a single perforating artery) (12). The different classification methods are set out in Table 2.

TABLE 2. Classification of ischemic stroke

TOAST [150]	Large artery atherosclerosis	Cardioembolism	Stroke of determined cause	Stroke of undetermined cause	Small-vessel occlusion
BAMFORD *et al* [151]	Total anterior circulation infarcts (TACI)	Partial anterior circulation infarcts (PACI)		Posterior circulation infarcts (POCI)	Lacunar infarcts (LACI)
PANTONI *et al* [12]	Non-lacunar stroke				Lacunar stroke

Classification of ischemic stroke based on pathophysiology (TOAST), location (Bamford *et al*), and phenotype (Pantoni *et al*).

As the terms suggest, lacunar stroke and cerebral small-vessel disease include stroke due to damage to the cerebral small arteries, veins, arterioles, and capillaries that leads to either ischemia (manifesting as white matter lesions or lacunar infarctions) or hemorrhage due to microbleeds (12). Cerebral small-vessel disease is believed to be the cause of acute ischemic stroke in 16–21% of all strokes (152,153). Cerebral small-vessel disease is caused by atherosclerosis in the small blood vessels, the accumulation of amyloid plaques, inflammatory disorders, or venous collagenosis (12). The clinical manifestations of both cerebral small-vessel disease and lacunar strokes are less severe when compared with those of large-vessel stroke; however, they are associated with cognitive impairment and dementia (154). An example of an ischemic stroke, as captured on a magnetic resonance image (MRI), is shown in Figure 1A.

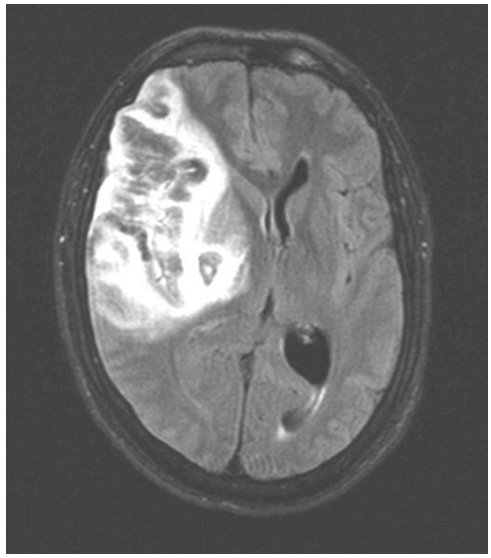

Figure 1A. Magnetic resonance image of a large cerebral infarction with hemorrhagic transformation, which is visible as the white area.

Hemorrhagic stroke. The two major hemorrhagic stroke subtypes are intracerebral hemorrhage and subarachnoid hemorrhage (155). Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes (156), and it is defined as bleeding into the brain parenchyma, which in some cases also extends into the ventricles (157). ICH can either be primary or secondary, depending on the underlying cause of the hemorrhage (156). Primary ICH, which accounts for 78–88% of all the cases of intracerebral hemorrhage, is caused by the spontaneous rupture of the small blood vessels due to hypertension or cerebral amyloid angiopathy (155). Secondary ICH is caused by the rupture of vascular malformations, of which arteriovenous malformations, cavernous angiomas, and aneurysms are the most common (156,158). The other, more minor causes of secondary ICH include trauma to the head, tumors in the brain parenchyma, coagulopathy due to drug use or hemostatic/hematologic disorders, toxins (e.g., cocaine), or the hemorrhagic transformation of ischemic stroke (11,156,159). Figure 1B illustrates an ICH as shown on a computed tomography (CT) image.

Figure 1B. Computed tomography image of an intracerebral hemorrhage, which is visible as the dense white area.

Subarachnoid hemorrhage (SAH), the other hemorrhagic stroke subtype, accounts for approximately 5% of all strokes. Of all the SAH, 85% are caused by the rupture of saccular aneurysms in the subarachnoid space. (11) In the general population, the remainder of SAH are caused by inflammation in the cerebral arteries, different coagulopathies (i.e., drug use or hemostatic/hematologic disorders), brain tumors, or toxins (160,161). Although both ICH and SAH are considered to be subtypes of hemorrhagic stroke, their etiology differs, and they are considered to be two

different kinds of stroke (148). However, the FinnDiane Study showed that SAH in individuals with type 1 diabetes differ from SAH in the general population, with the majority being of non-aneurysmal origin, mimicking the microvascular origin found in the case of ICH. Thus, the mechanisms and risk factors for these stroke subtypes appear to be rather similar in the presence of diabetes. (162)

Transient ischemic attack. A preliminary form of stroke is a transient ischemic attack (or TIA), which is defined as a brief focal loss of neurological function, thought to be caused by local ischemia, that lasts for less than 24 hours. In the case of a TIA, the ischemia in the brain is confined to a small area perfused by a specific artery. (163) This definition has, however, been questioned, since in many cases brain injury has been visible on the MRI of individuals with the classical symptoms of a TIA. Therefore, it has been proposed that a TIA should be defined as a "brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" (164). Irrespective of the inconclusive definitional criteria, a TIA should not be ignored, as this condition is considered to be a risk factor for stroke (165,166).

Pathophysiology of ischemic stroke. Ischemic stroke can be caused by thrombosis or embolus of the arteries, hypoperfusion, or venous thrombosis, which all lead to a compromised blood supply to the brain (167). Atherosclerosis causes the majority of such changes, and the development of atherosclerosis continues for decades before clinically significant changes are seen (168). The development of atherosclerosis begins with foam cells accumulating on the inside of the blood vessel walls, thereby leading to fatty streaks (169). As the years go by, those fatty streaks enlarge when extracellular lipids, such as cholesterol and lipoproteins, are oxidized and accumulate at this site in the blood vessel walls (170). Such changes to the vascular walls usually develop at the branching points of the blood vessels, as these areas are exposed to shear stress (169). Further changes to the blood vessel walls include the development of atherosclerotic plaques, that is, the lipid core becomes covered with smooth muscle cells and collagen (170). The plaques may continue to grow and eventually occlude the blood vessel lumen, leading to thrombosis and the occlusion of either the large blood vessels or single perforating arteries. The plaques may also rupture, thereby causing emboli and occlusion. The formation of atherosclerotic plaques also weakens the blood vessel walls, which may lead to the formation of aneurysms or hemorrhage into the cerebral tissue when the plaques rupture. (170,171)

In the case of extracranial carotid artery disease, the atherosclerotic plaques are formed mainly in the bifurcation area of the large carotid arteries that supply blood flow to the brain (172). The plaques may cause stenosis, which leads to

extensive disrupted cerebral blood perfusion, as explained above (170,171). The plaques can also rupture, thereby leading to emboli and the occlusion of smaller arteries located more distally (172). Irregular, lipid-rich plaques with necrotic cores are especially prone to rupture (173). The use of lipid-lowering agents in individuals with carotid artery stenosis diminishes the size and inflammation of the plaques, potentially leading to a diminished risk of stroke (174).

In terms of cardioembolic stroke, the thrombi or emboli formed in the cavities of the heart travel to the cerebral vasculature, where they cause the obstruction of the cerebral blood flow (150). Atrial fibrillation causes the dysfunction of the cardiac endothelium and disturbs the coagulation cascade, which promotes thrombus formation (175). The primary pathologic change seen in the case of atrial fibrillation is the formation of fibrosis and the dilation of the atrium (176). The left atrium has a tubular structure with an appendage, and it is the formation of this appendage that enhances the formation of blood clots (177). Atrial fibrillation also leads to decreased blood flow from the atrium. Together with an enlarged and dysfunctional left atrium, this leads to an activated intravascular coagulation-fibrinolysis cascade and the formation of blood clots. (178) Furthermore, atrial fibrillation also causes the release of the inflammatory and hemostatic markers that promote coagulation (179). The obstruction of the cerebral blood flow due to these thrombi causes similar damage to the cerebral tissue as seen in the case of atherosclerosis (170,171).

The disruption of the cerebral blood flow damages the brain. As the cerebral tissue is dependent on the continuous supply of oxygen due to the lack of a respiratory reserve, it is particularly vulnerable to ischemia. (167) The lack of oxygen initiates an ischemic cascade, leading to a lack of energy (180). The lack of energy causes the apoptosis of neurons, an inflammatory response, the phagocytosis of damaged tissue, and damage to the blood-brain barrier, which causes cerebral edema and damage to the cerebral tissue (171,180). The damaged tissue can be divided into the ischemic core, in which irreversible damage has occurred, and the surrounding penumbra, in which tissue salvation is feasible if the oxygen supply is restored. This penumbra is the primary target of the treatment of stroke. (181)

Pathophysiology of hemorrhagic stroke. Similar to ischemic stroke, hemorrhagic stroke causes hypoxia to the cerebral tissue due to the pressure of the expanding hematoma as well as the disrupted vascular supply (182). Furthermore, the released blood has toxic effects on the cerebral tissue, which causes an inflammatory reaction whereby the inflammatory cells and mediators of the immune system injure the cerebral tissue (183). If the bleeding continues, the increased intracerebral pressure may further restrict the cerebral blood flow (182). As previously described, ICH is generally caused by hypertensive arteriolosclerosis,

with high blood pressure causing smooth muscle cell proliferation, cell death, and collagen deposition, which leads to structurally weak blood vessel walls, and eventually, the rupture of the blood vessel (158). The second most common cause of ICH, that is, amyloid angiopathy, is a state wherein the accumulation of amyloid plaques in the blood vessel walls leads to the degeneration of the smooth muscle cells and weakened blood vessel walls similar to the hypertension-caused structural changes seen in the cerebral vasculature (184).

The pathophysiology of SAH differs from that of ICH in the general population because the vast majority of SAH arise due to the rupture of saccular aneurysms. These aneurysms usually develop at the branching points of the major arteries in the circle of Willis, which is the cerebral arterial circle that supplies the blood flow to the brain. The blood vessel walls in these branching points are thin and degenerate due to hemodynamic stress. Eventually, the walls of the aneurysms break, resulting in bleeding into the subarachnoid space, and in some cases, into the cerebral ventricles, as well as into the cerebral tissue. (161) The hemorrhage due to SAH causes similar hypoxia, inflammatory responses in the cerebral tissue, and increased intracranial pressure as seen in relation to ICH (161,182,183). A small number of SAH are non-aneurysmal and have a more similar microvascular pathophysiology to that of ICH (161). This is especially common in individuals with type 1 diabetes (162).

Hyperglycemia and stroke. Although stroke is generally considered to be a macrovascular complication, microvascular changes occur more frequently in those with hyperglycemia and diabetes than in the general population (20). Hyperglycemia and the diabetic milieu affect the microvasculature in the brain in several ways. For instance, chronic hyperglycemia, as is prevalent in those with diabetes, leads to the proliferation of the vascular smooth muscle cells (185), the thickening of the basement membrane of the capillaries (186), and the acceleration of the aggregation and adhesion of the platelets to the endothelium (187). These vascular changes lead to the dysfunction of the microvasculature in the brain, thereby affecting the permeability of the blood-brain barrier (188) and increasing angiogenesis (i.e., the growth of new blood vessels) (189). All these changes add up to hypoperfusion, hypoxia, and bleeding in the cerebral vasculature, which contribute to the pathogenesis of stroke in those with diabetes (190).

2.3.2 Diagnosis and treatment of stroke

Symptoms of stroke. The symptoms of stroke depend on which part of the brain is affected as well as on the extent of the damage to the brain tissue. The typical symptoms of stroke include sudden unilateral weakness and/or numbness, vision loss, double vision, speech difficulties, clumsiness, nausea and vomiting,

and vertigo. The atypical and associated symptoms may vary, and they are usually a consequence of the stroke itself. These symptoms include blindness in one or both eyes, memory loss, difficulty finding the appropriate word, difficulties swallowing, headaches, confusion, uncontrolled limb movements, and altered consciousness. (191,192)

Diagnosis of stroke. The diagnosis of stroke is clinical, and it is based on the persistent neurological symptoms and functional deficits (148). Neurological imaging is of great importance when it comes to determining the origin of a stroke, in addition to the location and extent of the resultant cerebral injury. The most common imaging technique is non-contrast CT. This technique is particularly useful for detecting ICH and, albeit to a lesser extent, SAH. (193) However, in the case of ischemic stroke, the sensitivity of this technique can prove inadequate, especially if the stroke is small or the imaging is performed less than 12 hours after the onset of symptoms (194,195). If an ischemic stroke is suspected, the imaging technique of choice is MRI, which has better resolution than CT (196,197). MRI is just as efficient as CT in relation to the detection of hemorrhages, both acute and prior (198). SAH can also be diagnosed by means of lumbar puncture and the finding of red blood cells in the cerebrospinal fluid (199). The use of this additional diagnostic method should be considered if more than six hours have elapsed since the onset of neurological symptoms (199,200). Essentially, the early detection and diagnosis of stroke are key to a better prognosis. Atypical stroke features and symptoms, uncertainty regarding the onset of symptoms, or normal imaging results can delay diagnosis. (201)

Treatment of ischemic stroke. The treatment of stroke depends on the subtype in question. The preferred treatment method for ischemic stroke is intravenous thrombolysis with recombinant tissue plasminogen activator in order to prevent the ischemic penumbra from becoming irreversibly damaged cerebral tissue (202,203). Timing is crucial, and treatment with intravenous recombinant tissue plasminogen activator should be initiated within nine hours of the onset of symptoms (202,204). In well-selected individuals in whom appropriate neurological imaging has been performed, this time limitation can be extended to up to 24 hours (202). Finland was one of the first countries in Europe to treat ischemic stroke with thrombolysis, with the first persons receiving such treatment in 1998 (205). Since then, a treatment protocol has been developed and the time to treatment has shortened rapidly, improving the prognosis of these people. In 2011, 94% of the people with ischemic stroke arriving at the neurology emergency room of the Helsinki University Central Hospital, which is a primary treatment facility, received thrombolysis within 60 minutes of arrival. (206) (Figure 2)

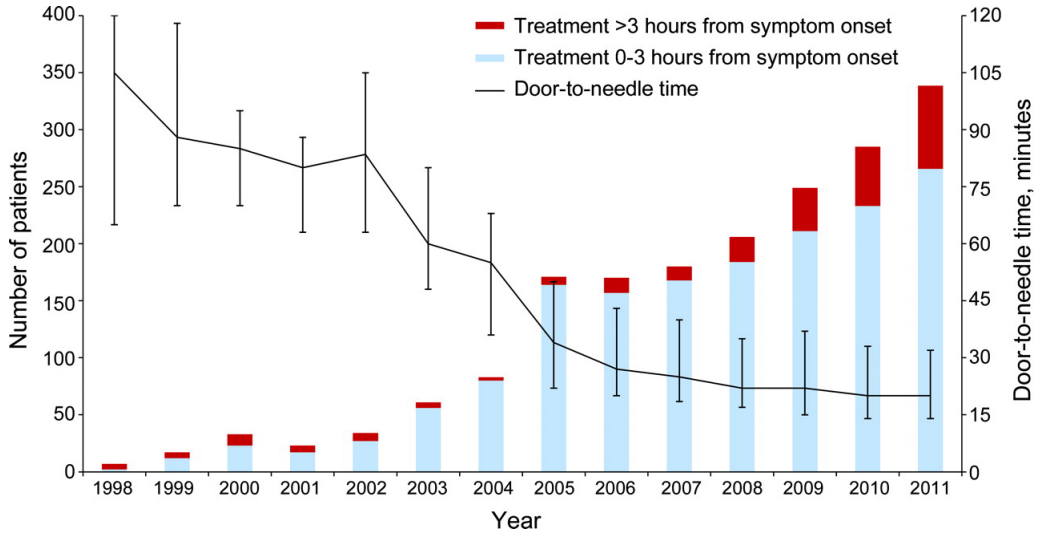

Figure 2. Number of annually treated patients and median door-to-needle times. Annual patients, with those treated beyond 3 hours in red (bars, left axis) and median door-to-needle time in minutes with interquartile range (line, right axis). Total n = 1,686. The projected number of patients for 2011 is based on the observed numbers of the first 6 months. Reprinted from Neurology, Meretoja *et al*, Reducing in-hospital delay to 20 minutes in stroke thrombolysis, pages 306 – 313. Copyright © 2012 American Academy of Neurology. Reprinted with permission from the American Academy of Neurology.

However, when it comes to proximal intracerebral artery occlusion, the intravenous recombinant tissue plasminogen activator fails to dissolve the occlusion (207). During the 1990s, local intra-arterial thrombolysis was first introduced to dissolve the occlusion in these arteries (208). Since then, the mechanical thrombectomy method, whereby a device designed to recanalize the occluded artery is inserted into the femoral artery, has been developed and is currently the treatment method of choice whenever intravenous thrombolysis proves ineffective or contradictory (209). To be effective, this treatment should be initiated within six hours of the onset of symptoms (210).

In the case of carotid stenosis, carotid endarterectomy is recommended in those symptomatic individuals with a stenosis of 50% or more (211). Carotid endarterectomy is a surgical procedure involving the removal of the carotid plaque and the reconstruction of the carotid artery (172). In individuals with a high risk of developing the complications of carotid endarterectomy, the stenting of the carotid artery may represent the treatment of choice (211). In this procedure, a mesh-like structure is inserted into the occluded area in the artery, which forces the lumen to open up (172).

Treatment of hemorrhagic stroke. With regard to hemorrhagic stroke, the treatment for the subtypes ICH and SAH differs. As with ischemic stroke,

the faster treatment is initiated, the better the outcome. The treatment goal for ICH is to diminish the hematoma and the perihematomal edema in an effort to minimize the cerebral damage. An important treatment strategy for ICH involves lowering the systolic blood pressure to < 140 mmHg in order to reduce the expansion of the hematoma. (212) In ICH caused by the use of anticoagulant therapies, anticoagulant reversal using therapeutic agents is recommended (213). For selected people with large hematomas, surgical intervention and the removal of the hematoma may be required (214). For SAH, both a reduction in blood pressure and the reversal of the anticoagulant treatment should be part of the immediate actions (215). The main treatment, however, is surgical, with the aim being to close the bleeding aneurysm by either coiling or clipping (216).

The secondary prevention of stroke is important, since the risk of suffering a recurrent stroke increases with time (201). To prevent a recurrent ischemic stroke, antiplatelet therapy is recommended in the presence of a TIA. The treatment of hypertension and dyslipidemia are important in relation to the secondary prevention of stroke. The blood pressure target is < 140/90 mmHg. However, in individuals with diabetes, the target is < 140/80 mmHg, and if albuminuria is present, it is < 130/80 mmHg. The LDL-cholesterol concentrations should be < 2.5–3 mmol/l in low- to medium-risk individuals, whereas in high-risk individuals, such as those with diabetes, the LDL-cholesterol concentrations should be < 1.8 mmol/l. (202)

2.3.3 Epidemiology of stroke

Incidence of stroke. The age-adjusted incidence of stroke varies between countries, with the highest incidence being found in Iran (689 per 100,000 person-years) and Ukraine (622 per 100,000 person-years), and the lowest in Kuwait (60 per 100,000 person-years) and Qatar (66 per 100,000 person-years). With regard to continents, the highest incidence of stroke is found in Eastern Europe and Asia, while the lowest incidence is found in Australia and Central America. (217) In Finland, approximately 21,000 individuals suffer a stroke each year (218), and the age-adjusted incidence is 240 per 100,000 person-years (217). Over the past few decades, the incidence of stroke has decreased by 40% in high-income countries. In low- to middle-income countries, however, the incidence has increased by more than 100% during the same period. (219)

Stroke is usually associated with an older age. Indeed, the majority (or two-thirds) of strokes occur in individuals over 70 years of age. (217) The incidence of stroke is higher in men (220); however, due to both longer life expectancy and older age, the total number of strokes in women is higher (221). The incidence of the major subtypes of stroke, namely ischemic and hemorrhagic stroke, also

differs, with the incidence of ischemic stroke being higher than the incidence of hemorrhagic stroke (222).

2.3.4 Epidemiology of stroke in people with diabetes

Incidence of stroke in people with diabetes. The age-adjusted incidence of stroke in individuals with type 2 diabetes varies between 550 per 100,000 and 1,190 per 100,000 person-years (223-225). The incidence of stroke in individuals with type 1 diabetes has been studied to a lesser degree. Data concerning the incidence of stroke in those with type 1 diabetes remain scarce, while data concerning the stroke subgroups are even scarcer due to the low number of individuals involved in the relevant studies (13,17). In the relatively large Nurses' Health Study conducted by Janghorbani *et al*, which involved 33 females with type 1 diabetes who had suffered incident strokes, the incidence of stroke was found to be 475 per 100,000 person-years (13), while in the Pittsburgh EDC Study, which involved 31 individuals with type 1 diabetes who had suffered incident strokes, the incidence was 310 per 100,000 person-years (17). The risk of stroke in those with type 2 diabetes is two- to five-fold higher when compared with the general population (13,15), and in men younger than 44 years of age, the risk can be up to 23-fold higher (226). In individuals with type 1 diabetes, Janghorbani *et al* found that the risk of stroke is six-fold higher when compared with the general population (13), while Soedemah-Muthu *et al* found the risk of stroke to be four-fold higher in men and five-fold higher in women (123). The risk of stroke in younger individuals (under the age of 50) with type 1 diabetes has been determined to be almost 20-fold higher (16).

Stroke occurs at a younger age in individuals with diabetes than in the general population. Those with type 2 diabetes are, on average, three years younger than those without diabetes at the time of their incident stroke. (227) Information regarding the age at the time of stroke in those with type 1 diabetes is, again, limited. The mean age at the time of stroke in individuals with type 1 diabetes in the study by Janghorbani *et al* was 63.4 years, which was 4.5 years younger than in the general population (13). The age at the time of stroke was even younger in the Pittsburgh EDC Study, where the mean age was 40.2 years (17). Men with type 1 diabetes seem to be at a high risk of stroke some 10–15 years earlier than the general population, while the risk increases even earlier in women with type 1 diabetes (123).

Stroke subtypes. Individuals with type 2 diabetes have a higher risk of suffering an ischemic stroke than individuals without diabetes, while the risk of suffering a hemorrhagic stroke in those with type 2 diabetes is not increased when compared with the general population (13,228). For individuals with type 1 diabetes, not only is the risk of ischemic stroke increased when compared with the general

population, as the risk of hemorrhagic stroke is also increased (13). The risk of ischemic stroke in these individuals is 3.3- to 8.2-fold higher, while the risk of hemorrhagic stroke is 2.5- to 4.5-fold higher, when compared with the general population (13,229).

The ratio of the major stroke subtypes in individuals with diabetes is similar to that in the general population, with approximately 80% of strokes being of ischemic origin and 10% of hemorrhagic origin (230). However, with regard to the etiology, cerebral small-vessel disease is more prominent in those with diabetes than in the general population. In young individuals under the age of 50, cerebral small-vessel disease has been found in 10% of incident ischemic strokes in the general population, while in individuals with type 2 diabetes, the corresponding percentage of cerebral small-vessel disease was found to be 42%. In those with type 1 diabetes, the presence of cerebral small-vessel disease was even higher, standing at 61%. (20) In another study, Shah *et al* showed that lacunar stroke was the most common stroke subtype in individuals with type 2 diabetes, accounting for 44% of all strokes (231). In a recent study by Thorn *et al*, cerebral small-vessel disease was found to be more common in young neurologically asymptomatic individuals aged 18–50 years who had type 1 diabetes than in age-matched controls. Moreover, the presence of cerebral microbleeds was especially noticeable in those with type 1 diabetes. (232)

2.3.5 Risk factors for stroke and its subtypes

The strongest and most well-known independent risk factors for stroke are hypertension (21), an older age (22), the male sex (22,233), atrial fibrillation (23), smoking (22,234), and diabetes, both type 1 and type 2 (13,14,235). The findings of studies regarding the role played by hypercholesterolemia in relation to the risk of stroke are somewhat inconsistent, with a clearer association between high blood cholesterol and an increased risk of stroke being seen in individuals younger than 45 years (236). However, the risk of stroke decreases with statin therapy (237).

The metabolic syndrome is also an independent risk factor for stroke, increasing the risk 1.8- to 2.3-fold even without the presence of diabetes or impaired glucose tolerance (25,140). Linked to this, insulin resistance (238) and obesity (239,240) both increase the risk of stroke. Other lifestyle factors, including high alcohol consumption (241,242), and a lack of physical activity (240,243), also increase the risk of stroke. All these factors are more often seen in individuals living in industrial countries; therefore, the risk factors for stroke vary globally and are somewhat region-specific (240). Other, less well-known risk factors for stroke include aural migraine (244), chronic kidney disease (245), the use of certain substances (i.e., amphetamine and cocaine) (246,247), chronic inflammation (248), psychosocial factors (i.e., depression and stress) (249,250), and genetic

susceptibility (251). Additionally, previously suffering a stroke or TIA increases the risk of suffering a new stroke (32,252).

Subtypes of stroke. The risk factors for the subtypes of stroke differ somewhat. The most well-known risk factors for ischemic stroke are hypertension, diabetes, being older than 55 years, atrial fibrillation, smoking, and the male sex (253). In addition, weakened kidney function (254) and non-HDL cholesterol (255) are also associated with an increased risk of this stroke subtype. The risk factor profile for lacunar stroke is similar to that for ischemic stroke; however, hypertension and diabetes seem to be more common in lacunar strokes, while atrial fibrillation is more common in non-lacunar strokes (256). For ICH, some risk factors similar to those for ischemic stroke have been found. These include an older age, hypertension, and diabetes (253). Smoking is more strongly associated with SAH than with ICH (257,258), while the protective role of the female sex seen in relation to ischemic stroke is not observed in relation to ICH (259). Moreover, being on dialysis increases the risk of ICH more than eight-fold (260). The use of oral anticoagulation medication (261,262) and the presence of brain tumors (263) are also associated with an increased risk of hemorrhagic stroke. With regard to cholesterol and ICH, low concentrations of LDL-cholesterol, independently of statin use, have been shown to increase the risk of this subtype. More specifically, LDL-cholesterol concentrations < 1.8 mmol/l double the risk of ICH. (264)

2.3.6 Risk factors for stroke and its subtypes in people with diabetes

Type 2 diabetes. The risk factors for stroke in individuals with type 2 diabetes have been elucidated in several studies. Most such risk factors are similar to those seen in the general population, that is, hypertension, an older age, the male sex, atrial fibrillation, and the metabolic syndrome all independently increase the risk of stroke in individuals with type 2 diabetes. (24,25,265) Smoking (266) and having suffered a previous stroke or TIA (225) also independently increase this risk. Furthermore, higher HbA_{1c}, which is a marker of poor glycemic control, is associated with an increased risk of stroke in those with type 2 diabetes (267). When it comes to microvascular complications and the stroke risk, a slight decrease in the glomerular filtration rate, which can be used to estimate decreased kidney function, increases the risk of stroke (268). Moreover, the presence of both micro- and macroalbuminuria independently increase the risk of stroke in individuals with type 2 diabetes (24,265,269). Interestingly, retinopathy has proved to be an independent risk factor for ischemic stroke in those with diabetes. This study did not, however, take diabetic nephropathy into account. (270) A higher neutrophil-to-lymphocyte ratio, which can be used as a marker of systemic inflammation, is associated with a higher risk of ICH in individuals with type 2 diabetes (271).

Dyslipidemia and cholesterol do not seem to be associated with the risk of stroke in those with type 2 diabetes (24,265).

Type 1 diabetes. For individuals with type 1 diabetes, only a few studies have investigated the risk factors for stroke. In contrast to the general population and those with type 2 diabetes, no sex-related difference is seen in individuals with type 1 diabetes when it comes to the risk of stroke (123). In the Pittsburgh EDC Study, a longer duration of diabetes, higher non-HDL cholesterol, and overt diabetic nephropathy all independently increased the risk of any type of stroke. Additionally, elevated systolic blood pressure and higher HbA_{1c} increased the risk of stroke if no adjustment was made for diabetic nephropathy. (17) In a small study conducted by Davis *et al*, which investigated six incident strokes in individuals with type 1 diabetes, higher HbA_{1c} and low HDL-cholesterol emerged as risk factors for stroke (272). The only study to have assessed the risk factors for stroke subtypes in individuals with type 1 diabetes is the Pittsburgh EDC Study. In relation to 21 ischemic strokes, the baseline predictors proved to be the diabetes duration, systolic blood pressure, non-HDL cholesterol, white blood cell count, and pulse. In the same study, the baseline predictors of hemorrhagic stroke were the diabetes duration, higher HbA_{1c}, and elevated diastolic blood pressure. Notably, only eight hemorrhagic strokes were included in the analyses. (17) The risk factors for stroke in the general population, as well as in individuals with type 1 and type 2 diabetes, are summarized in Table 3.

TABLE 3. Risk factors for any type of stroke in the general population and in individuals with type 2 and type 1 diabetes

	General population	Type 2 diabetes	Type 1 diabetes
Hypertension [17,21,24,265]	+ +	+ +	+ +
Age/Duration of diabetes [17,22,24,265]	+ +	+ +	+ +
Male sex [22,24,123,233,265]	+ +	+ +	–
Atrial fibrillation [23,24]	+ +	+ +	?
Smoking [22,230,234,266]	+ +	+	?
Diabetes [13,235]	+ +	NA	NA
Cholesterol [17,24,236,237,265,272]	+ –	–	+
Metabolic syndrome [25,140]	+	+	?
Insulin resistance [238]	+	NA	?
HbA_{1c} [17,267,272]	NA	+	+ +
Obesity [24,239,240]	+	–	?
Alcohol consumption [241,242,273]	+	+ –	?
Lack of physical activity [24,240,243]	+	–	?
TIA/Previous stroke [32,230,252]	+	+	?
Chronic kidney disease [17,245,265,268]	+	+	+
Retinopathy [270]	NA	+ –	?
Chronic inflammation [17,248,271]	+	+	+
Depression and stress [249,250,274]	+	+	?
Aural migraine [244]	+	?	?
Genetic factors [251,275,276]	+	+	+ –
Substance abuse [246,247]	+	?	?

NA = not applicable for the group in question. TIA = transient ischemic attack, HbA_{1c} = glycosylated hemoglobin A_{1c}.

Other risk factors. Haptoglobin (Hp), a plasma protein-binding free hemoglobin that inhibits oxidative tissue damage, has been found to affect the risk of cardiovascular disease, including stroke, in individuals with type 2 diabetes. Haptoglobin is present as three genotypes: Hp 1-1, Hp 1-2, and Hp 2-2. The Hp 2-2 genotype increases the risk of cardiovascular disease in those with type 2 diabetes, while no such increase is seen in individuals without diabetes. (275) Costacou *et al* studied this effect in individuals with type 1 diabetes, and no increased risk of stroke was observed for the Hp 2-2 genotype. Yet, a borderline increased risk of stroke was found for the Hp 1-1 genotype. (276) Further studies on this potential risk factor are needed before any conclusions can be drawn.

2.3.7 Blood pressure, salt intake, and risk of stroke in people with diabetes

Elevated blood pressure represents one of the strongest risk factors for stroke in the general population (21,277). The risk of stroke decreases in a linear fashion with antihypertensive treatment down to blood pressure levels of 115/75 mmHg, while no beneficial effect is found at lower blood pressure levels. This decreased risk of stroke is seen in both ischemic stroke and ICH, as well in relation to both sexes. In addition, the risk decreases when any type of antihypertensive agent is used. (21) The different blood pressure variables (i.e., systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure) all independently increase the risk of stroke in the general population (28). However, the strongest variable associated with the stroke risk appears to be the systolic blood pressure, while the pulse pressure is associated with the weakest risk of stroke (28,278,279). The association with stroke is not as strong for the diastolic blood pressure as for the systolic blood pressure. This is possibly due to the fact that the diastolic blood pressure does not increase with age in the same way that the systolic blood pressure does due to arterial stiffness; in contrast, it increases up to ~ 60 years of age and then decreases. (280,281) In individuals with type 1 diabetes, this arterial stiffness develops 15–20 years earlier than in the general population (282).

Blood pressure and type 2 diabetes. Hypertension is one of the strongest risk factors for stroke in individuals with type 2 diabetes (24,265). When it comes to the different blood pressure variables, there is some evidence that the pulse pressure is a better predictor of the risk of cardiovascular disease in those with diabetes than the systolic or diastolic blood pressure (283). A pulse pressure ≥ 75 mmHg, when compared with < 75 mmHg, has also been found to increase the risk of stroke 1.5-fold in those with type 2 diabetes (284). Moreover, while the association between the systolic blood pressure and the risk of stroke is linear in the general population (21), some studies indicate that the relationship could be J-shaped in those with type 2 diabetes (29,285). Zhao *et al* showed that the risk of any type of stroke increased when the systolic blood pressure was < 110 mmHg or > 160 mmHg. The diastolic blood pressure also showed a J-shaped relationship with the stroke risk in the same study. In fact, the risk was increased at diastolic blood pressure levels < 65 mmHg or > 100 mmHg. This J-shaped phenomenon was seen mostly in younger individuals under the age of 60. (29)

Blood pressure and type 1 diabetes. When it comes to type 1 diabetes, the systolic blood pressure has proved to be an independent risk factor for stroke with a hazard ratio of 1.4 (per standard deviation of the systolic blood pressure, which, in this case, was 16) only when no adjustment is made for diabetic nephropathy, which correlates strongly with the blood pressure. The same was seen for the

ischemic stroke subtype, where the systolic blood pressure increased the risk 1.6-fold. In contrast, for hemorrhagic stroke, the diastolic blood pressure independently increased the risk two-fold in the Pittsburgh EDC Study, while the systolic blood pressure was not significant. (17) Information concerning how the mean arterial pressure and the pulse pressure affect the risk of stroke in individuals with type 1 diabetes is lacking, and no studies have investigated the linearity between the blood pressure and the risk of stroke in these individuals.

Salt intake and risk of stroke. An individual's blood pressure is closely linked to their use of salt (or sodium intake). The gold standard measurement of an individual's sodium intake involves measuring the 24-hour urinary sodium excretion, since dietary questionnaires are prone to underestimate the salt intake (286). An increased sodium intake raises the blood pressure by disturbing the sodium and potassium metabolism within the kidneys, thereby leading to the contraction of the smooth muscle cells and increased vascular resistance. The disturbed kidney metabolism also results in increased extracellular fluid and blood volume. (287) This causes hypertension, which eventually leads to an increased risk of cardiovascular disease and stroke. Tuomilehto *et al* found that increased urinary sodium excretion increases the risk of all-cause mortality and coronary heart disease in the general population; however, no increased risk of stroke was found .(288) In more recent studies, a higher sodium excretion rate has been shown to independently increase the risk of stroke. Indeed, the risk was 1.5- to 3.0-fold higher when the sodium intake exceeded eight grams/day. (289,290) Interestingly, there is some evidence of a J-shaped relationship between the risk of cardiovascular events and an individual's sodium intake. In a study by Lamelas *et al*, the risk of cardiovascular events, including stroke, increased when the sodium intake exceeded seven grams/day, or if it was less than three grams/day. (291) Furthermore, a higher potassium intake has been shown to have a protective effect against both cardiovascular disease and stroke (292,293). There is also evidence that the ratio of sodium and potassium affects the risk of cardiovascular disease even more than the intake of sodium and potassium alone (294).

Not many studies have investigated the link between the salt intake and cardiovascular disease in individuals with diabetes, and the findings that are available are somewhat inconsistent when compared with those concerning the general population. Paradoxically, lower urinary sodium excretion has been found to increase the risk of all-cause and cardiovascular mortality in those with type 2 diabetes (295), while higher urinary potassium excretion was observed to decrease the incidence of cardiovascular complications, including stroke, in individuals with type 2 diabetes (296). Lower urinary sodium excretion was also seen to increase the risk of all-cause mortality in individuals with type 1 diabetes. Moreover, the association was found to be non-linear, and the risk started to increase when the

urinary sodium excretion exceeded 187 mmol/day, which equals an intake of approximately 11 grams of salt per day. (297) There is still a lack of information concerning the relationship between urinary sodium and potassium excretion and the risk of stroke in individuals with type 1 diabetes.

2.3.8 Prognosis of stroke

The incidence of stroke has decreased over the past 50 years, although the risk of stroke has remained the same (220). The mortality rate associated with stroke has decreased alongside the incidence. However, this means that the number of survivors left with disabilities after suffering strokes has increased. In 2013, there were 26 million survivors of strokes worldwide. The risk of being affected by stroke in some way (i.e., death by stroke, disability, or survival after stroke) almost doubled from 1990 to 2013. A concerning finding was that the number of young individuals aged 20–64 years who were affected by stroke increased during the same period, mostly due to the increased prevalence of hemorrhagic stroke. (298)

Consequences of stroke. Even though the mortality rate associated with stroke has decreased, stroke survivors still have to deal with the consequences of stroke. Disability in some form or other affects the majority of survivors, and the symptoms depend on the size and location of the brain tissue lesion. The symptoms can be of a physical, emotional, or mental nature, and they can persist from a few hours up to the rest of an affected individual's life. (299) Many disabilities are similar to the acute symptoms of stroke, as discussed in section 2.3.3. Furthermore, 5–20% of all individuals who suffer a stroke are afflicted with seizures, and less commonly, epilepsy. This risk increases with age, and it is more common following a hemorrhagic stroke. (300) Dementia and cognitive impairment are also disabilities that affect the individual's life after stroke. These occur in 10–30% of stroke survivors, and an older age increases the risk. (301) Emotional disabilities after stroke can be a consequence of dementia as well as of the stroke itself. These disabilities include mood swings, loss of emotional control, and emotional flattening. (302) Furthermore, psychiatric disorders, such as depression and anxiety, are common after stroke; depression occurs in approximately 30% of all survivors after stroke (303), while 10% of survivors experience anxiety disorders (304).

Survival after stroke. The mortality rate associated with stroke is high, with more than 25% of individuals who suffer an incident stroke dying within the first year after the stroke (30). After that time, the annual death rate varies between 5% and 10%. The main causes of death are a recurrent stroke, cardiovascular disease, or complications following the initial stroke. (305,306) Only 20% of those who

survive an incident stroke are still alive 10 years after the initial stroke (306). The five-year mortality rate is lower (6–8%) in younger individuals under the age of 50 who suffer an incident stroke (31,307). Mortality after stroke is also affected by the type of stroke, and hemorrhagic stroke is associated with a poorer outcome than ischemic stroke. Of those who suffer a hemorrhagic stroke, 21–22% die within a month of the initial stroke, while the corresponding percentage is 4–8% for those who suffer an ischemic stroke. (307,308) Yet, this is only true during the first few months after stroke. The difference in survival after hemorrhagic or ischemic stroke begins to decrease at three months after the stroke, while after five months, no difference in survival is seen between the stroke types. (309,310) When it comes to the subtypes of ischemic stroke, non-lacunar infarctions have a higher mortality rate than lacunar infarctions, that is, a 10–20% 30-day mortality rate when compared with a 0–2% rate (311). Again, the higher mortality rate is evident during the first 30 days after the initial stroke, and after that point, the differences in survival between the ischemic stroke subtypes diminishes (312).

Predictors of mortality. Naturally, an older age is one of the strongest predictive factors for poor survival following a stroke in the general population (31,32,313). Other predictors of poor survival include the male sex, the presence of a TIA prior to the first stroke, coronary heart disease and heart failure, and the heavy use of alcohol (31,32,305,313). Additionally, a recurrent stroke, as well as institutionalization and long-term disability, predict poor survival (31,313). Depression at the time of the first stroke has also been shown to increase the risk of mortality for up to one year after the stroke (314).

Another strong predictor of mortality following an incident stroke is diabetes (32,315), especially type 1 diabetes in younger individuals under the age of 50 (31). Diabetes independently increases the risk of long-term mortality by up to four times in individuals who suffer an incident stroke (31). Impaired kidney function, measured as the eGFR, increases the risk of mortality after stroke when the eGFR declines below 60 ml/min/1.73m^2. Further, impaired kidney function predicts a new cardiovascular event after an incident stroke. (316)

Survival according to stroke subtype. As stated above, hemorrhagic stroke is associated with poorer survival than ischemic stroke. The mortality of hemorrhagic stroke is 1.6-fold higher when compared with ischemic stroke. (32) The predictors of survival after a stroke are somewhat different for the ischemic and hemorrhagic stroke subtypes. For both, an older age and diabetes independently increase the risk of a poor outcome. (310,317,318) For ischemic stroke, the presence of atrial fibrillation, smoking, cardiac failure, and cerebral small-vessel disease predict mortality (310,319). In young adults under the age of 50 who suffer an ischemic stroke, type 1 diabetes is a predictor of a poor outcome following an

incident stroke (320). Moreover, for these young individuals, impaired kidney function also increases the risk of poor survival (321,322). Diabetes, whether type 1 or type 2, is independently associated with poor long-term survival in individuals who suffer an ICH (323). No difference in relation to sex has been found in terms of ischemic stroke and survival (310), while for hemorrhagic stroke, the results are contradictory. Bhalla *et al* found the female sex to be associated with a poor prognosis (310), while in other studies, the male sex was found to be associated with a worse outcome (324,325). Furthermore, heart failure is also a predictor of mortality in the case of hemorrhagic stroke (324).

2.3.9 Prognosis of stroke in people with diabetes

Hyperglycemia and higher HbA_{1c}, without the presence of diabetes, increase the risk of mortality after an incident ischemic stroke. More specifically, HbA_{1c} concentrations more than 37 mmol/mol at the time of the stroke increase the risk of all-cause mortality one year after the stroke, and the risk is almost three-fold higher if the HbA_{1c} concentration is more than 55 mmol/mol. (326) When comparing survival after stroke in individuals with and without diabetes, no differences in the short-term risk of mortality (i.e., death within a few months of the stroke) has been detected (327,328). However, the long-term risk of mortality (i.e., death within years of the incident stroke) is almost two-fold higher in individuals with diabetes (227,328,329). In addition, recovery after a stroke is slower if diabetes is present at the time of the stroke (227).

Type 2 diabetes. The predictors of stroke in individuals with type 2 diabetes differ to some extent with the predictors in individuals without diabetes. In terms of hemorrhagic stroke, an older age and atrial fibrillation predict a poorer outcome after stroke (330). If the stroke is of ischemic origin, the presence of atrial fibrillation, an older age, congestive heart disease, and nephropathy all predict immediate poor survival in individuals with diabetes (331). Proteinuria has been shown to be one of the strongest predictors of severe disability and mortality after an ischemic stroke in those with diabetes. The risk of a poor outcome is more than four-fold higher even after adjusting for age and the systolic blood pressure. In the same study, the use of angiotensin receptor blockers as antihypertensive medication prior to stroke was found to have a protective effect. (33)

Type 1 diabetes. Mortality due to cerebrovascular disease in individuals with type 1 diabetes is increased in both sexes. When compared with the general population, the risk of mortality is 3.1-fold higher in men and 4.4-fold higher in women with type 1 diabetes. (17) Only one study has further explored the predictors of the outcome after stroke in individuals with type 1 diabetes. In

the Pittsburgh EDC Study, which investigated 31 incident strokes, survival after stroke was found to be poor. Among the participants, 19 died during the mean follow-up period of 15.4 years. The one-year survival rate was 81%, and more than half the participants died within five years after the stroke. Less than 10% of participants were still alive ten years after the stroke. Moreover, hemorrhagic stroke was associated with a poorer prognosis than ischemic stroke. The one-year survival rate was 95% for ischemic stroke and 50% for hemorrhagic stroke, while the five-year survival rate was 52% for ischemic stroke and 25% for hemorrhagic stroke. Poor glycemic control, expressed as higher HbA_{1c} concentrations, was a predictor of poor survival. No association between renal dysfunction, proteinuria, and mortality after stroke was found. (17)

3 AIMS OF THE STUDY

The aims of this thesis were as follows:

I To elucidate the incidence of stroke and its subtypes in individuals with type 1 diabetes as well as to study the impact of diabetic nephropathy and severe diabetic retinopathy on the risk of stroke and its subtypes.

II To investigate the independent risk factors for stroke and the ischemic stroke, lacunar infarction, and hemorrhagic stroke subtypes in a large sample of individuals with type 1 diabetes.

III To assess the impact of sodium intake and the different blood pressure variables and levels on the risk of stroke and the ischemic and hemorrhagic stroke subtypes in individuals with type 1 diabetes as well as to explore the linearity of that risk.

IV To study the prognosis of individuals with type 1 diabetes who have suffered an incident stroke as well as to identify the predictors of survival following a stroke in those individuals.

4 PARTICIPANTS AND STUDY DESIGN

4.1 The FinnDiane Study

All the participants in the studies included in this thesis are part of the FinnDiane Study, which is a nationwide, multicenter study. The study was launched in November 1997, and the first participants were recruited in January 1998. The recruitment of participants is ongoing, and follow-up data have been collected since 2004. The aim of the FinnDiane Study is to identify the genetic, environmental, and clinical risk factors for micro- and macrovascular complications in individuals with type 1 diabetes, with a focus on diabetic nephropathy. By the end of August 2020, some 5,491 adult individuals with type 1 diabetes in Finland had participated in the study, which represents approximately 10% of all individuals with type 1 diabetes in Finland. The study includes 78 study centers. All five university hospitals, all 16 central hospitals, 26 other hospitals, and 31 primary health-care center units in Finland have participated in the study (as listed in the Appendix). The recruitment took place during regular diabetes-related visits. The geographic distribution of the participating study centers is shown in Figure 3. The distribution follows the population density of Finland, with the majority of the population living in the south of the country. The local ethics committee of each center approved the study protocol, and the study was conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent prior to participating in the study. All the research files used in the study are coded with identification numbers, and only the FinnDiane researchers are familiar with the participants' personal information.

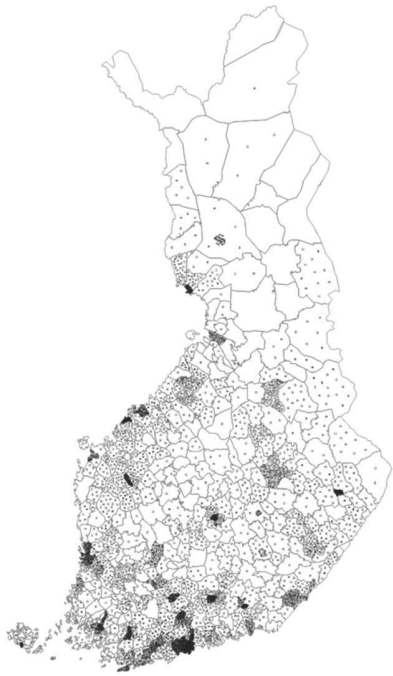

Figure 3. Distribution of the FinnDiane Study participants. Each dot represents one FinnDiane participant. The distribution is similar to the geographical distribution of the population of Finland, with most people living in the southern parts of the country.

4.2 Identification and classification of strokes

Identification of strokes. The participants in the FinnDiane Study who suffered a stroke were identified from three different sources. First, from the FinnDiane questionnaires. Second, from death certificates retrieved from Statistics Finland by March 2010 for Studies I, II, and IV as well as by December 2012 for Study III. Third, from the National Care Register of Health Care (Hilmo), as based on the tenth revision of the International Classification of Diseases (ICD) codes I60–I64, by December 2009 (Studies I, II, and IV) or by December 2012 (Study III). For each identified stroke, we ordered medical records, CT images, and MRIs of the participants with an identified stroke from the hospitals where they had been treated.

Classification of stroke. Based on the gathered medical files and CT images or MRIs, as well as on autopsy findings where appropriate, all the strokes that presented with clinical symptoms were identified and preliminarily classified as hemorrhagic or ischemic stroke by myself and my supervisor, Lena Thorn. The

definite classification of the strokes into subtypes was performed by Jukka Putaala (HUS, Department of Neurology), an experienced stroke neurologist, with the help of Ron Liebkind (HUS, Department of Neurology). The ischemic strokes were further classified as either lacunar or non-lacunar infarction. An experienced neuroradiologist (Oili Salonen, HUS, Department of Neuroradiology) was consulted in relation to the classification of the strokes if problems with the classification occurred. We defined lacunar infarction as one of the known lacunar syndromes with a brain imaging lesion corresponding to the occlusion of a single perforating artery. When no such lesion was visible, the classification relied on the established criteria of unilateral motor or sensory signs, or a combination of the two, involving at least two out of three body parts (face, arm, and leg) without the disturbance of either cortical functions or consciousness (152). The hemorrhagic transformation of an ischemic stroke was classified as an ischemic stroke. Hemorrhagic strokes were further classified as either SAH or ICH, which were then further classified into deep spontaneous hemorrhage or lobar spontaneous hemorrhage. A stroke was defined as fatal if the participant died within 30 days of onset of symptoms.

A more detailed description of the strokes at baseline, as based on the classification of ischemic and hemorrhagic stroke, is available in Table 4.

TABLE 4. Stroke data concerning ischemic and hemorrhagic stroke

	Ischemic stroke	**Hemorrhagic stroke**
n	**105**	**44**
Age at stroke (years)	51.2 ± 9.6	48.7 ± 7.7
Follow-up time to stroke (years)	5.1 ± 2.9	4.8 ± 2.8
Stroke fatality	4 (4%)	16 (36%)*
Lacunar infarction	58 (55%)	-
Deep spontaneous hemorrhage	-	25 (57%)
Lobar spontaneous hemorrhage	-	4 (9%)
Hemorrhage in subarachnoid space	-	15 (34%)
Diagnostic imaging		
MRI performed	28 (27%)	11 (25%)
CT performed	102 (97%)	41 (93%)
Angiography of cervicocerebral arteries	21 (20%)	15 (34%)
Echocardiogram performed	26 (25%)	2 (5%)*
Carotid ultrasound performed	55 (52%)	0 (0%)*
Hospital		
University	45 (43%)	27 (61%)*
Central	53 (50%)	14 (32%)*
District	6 (6%)	0 (0%)
Died at home	1 (1%)	3 (7%)*

Data are presented as mean ± standard deviation or number of cases (%). * = $p < 0.05$ when compared with ischemic stroke. MRI = magnetic resonance imaging, CT = computed tomography. Adapted from Hägg *et al*, Study I.

4.2.1 Participant selection for Studies I, II, and IV

For Studies I, II and IV, we included all the participants with type 1 diabetes included in the FinnDiane Study database who had no history of stroke at baseline and for whom there was complete information on the stroke suffered during follow-up available up to the end of 2010. Any FinnDiane participants who had suffered a stroke prior to the first FinnDiane visit, which was also termed a baseline stroke, were excluded. We also excluded 432 participants who did not meet the criteria for type 1 diabetes, as defined in section 5.1.2. Due to unclear information on the incident stroke, a further 15 participants were excluded. In addition, two participants were excluded due to subdural hemorrhages, one due to traumatic hemorrhage, one due to perinatal cerebral hemorrhage, and one due to hypertensive encephalopathy. Furthermore, 43 participants without complete information concerning severe diabetic retinopathy were also excluded. This resulted in a total of 4,083 participants, of whom 149 participants had suffered an incident stroke (Figure 4).

The follow-up time for Studies I, II, and IV was calculated from the baseline visit until the final date the participants were known to be free of stroke, until the time of death, or until the date of the first stroke for those who suffered a stroke.

4.2.2 Participant selection for Study III

For Study III, we included the original 4,083 participants from Studies I, II, and IV. Additional information on incident strokes suffered from 2011–2012 was available for Study III, which was obtained from the same sources as for Studies I, II, and IV (see section 4.2). This resulted in a total of 4,105 participants with type 1 diabetes, of whom 202 had suffered an incident stroke. Furthermore, for Study III, we included additional information from after the incident stroke. This follow-up information consisted of hard cardiovascular endpoints, namely acute myocardial infarction, coronary artery bypass surgery, coronary angioplasty, stroke, or death due to cardiovascular- or diabetes-related causes, all of which were collectively referred to as a composite vascular endpoint. The follow-up information after the incident stroke for each participant was collected from medical records, death certificates until August 2012, the FinnDiane database, and Hilmo, as based on the tenth revision of the ICD, by December 2011 for cardiovascular events and by December 2012 for strokes.

The same exclusion criteria as applied in relation to Studies I, II, and IV were applied with regard to these participants. Due to unclear information on the stroke, 11 participants were excluded. Furthermore, 151 participants without information on the systolic blood pressure, three participants without information on the diastolic blood pressure, and 32 participants without information on the antihypertensive medication were excluded. Two participants without any event

during the follow-up period died from an unknown cause and so were also excluded (Figure 4).

The follow-up time was calculated from the date of the incident stroke until the date of the second stroke, the first hard cardiovascular endpoint, or death, or until the final date the participants were known to be free of a composite endpoint (i.e., December 2012).

The selection of participants for the different studies is illustrated in Figure 4.

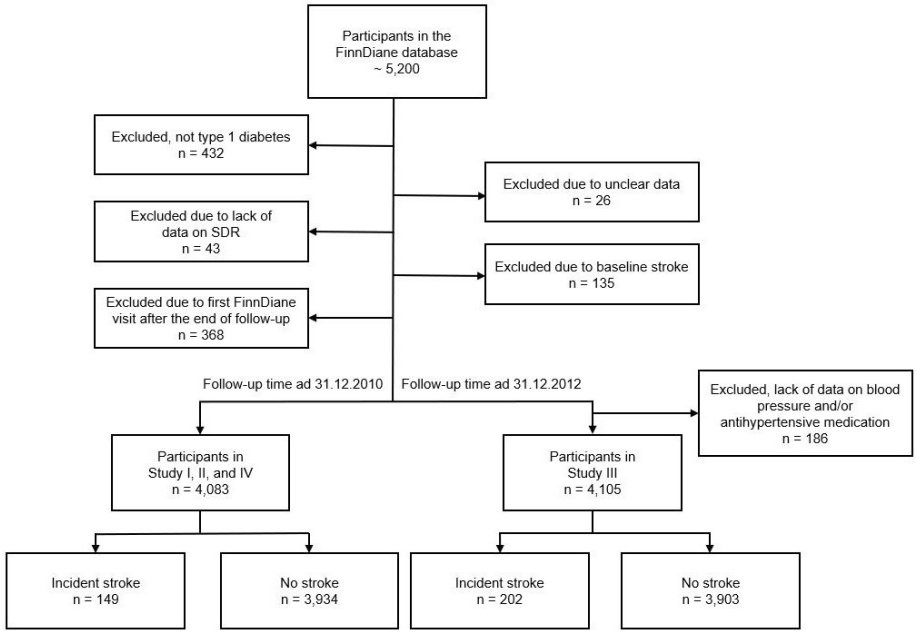

Figure 4. Flow chart of participant selection for the studies. SDR = severe diabetic retinopathy.

5 METHODS

5.1 FinnDiane Study protocol

5.1.1 FinnDiane Study visit

At baseline, the participants all underwent a thorough clinical examination during a regular visit to the attending physician. Both the attending physician and the participant completed standardized questionnaires regarding the participant's medical condition, medical history, medication, diabetes duration, smoking habits, and lifestyle. Measurements of the participant's weight, height, waist and hip circumferences, and blood pressure were taken during the visit. In addition, blood samples were drawn, and either overnight or 24-hour urine collections were performed. These samples were sent to the central laboratory of the FinnDiane Study, and more biochemical variables were measured centrally at the Helsinki University Hospital laboratory.

5.1.2 Definitions of type 1 diabetes

We defined type 1 diabetes as diabetes diagnosed before the age of 40 as well as permanent insulin medication commenced within a year following the diagnosis.

5.1.3 Anthropometric measurements

Each participant's weight was registered to the closest 0.1 kg, while their height was registered to the closest 1 cm. The body mass index (BMI) was calculated as the participant's weight divided by their height squared (kg/m^2). The waist circumference was measured midway between the lowest rib and the iliac crest, while the hip circumference was measured at the widest part of the gluteal region. The WHR was calculated as the waist circumference divided by the hip circumference.

5.1.4 Blood pressure measurements

Each participant's office blood pressure was measured twice in the sitting position, with ten minutes of rest before the first measurement was taken. The mean values of these two measurements were calculated for both the systolic and diastolic blood pressures. The pulse pressure was calculated as the systolic blood pressure – the diastolic blood pressure. The mean arterial pressure was calculated as the diastolic

blood pressure + ⅓ the pulse pressure. The blood pressure measurements were performed using either a manual mercury sphygmomanometer or a standardized automated blood pressure device. Antihypertensive medication was defined as the use of any antihypertensive agent, that is, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, β blockers, diuretics, or other antihypertensive agents.

5.1.5 Definition of the metabolic syndrome

The metabolic syndrome was defined according to both the National Cholesterol Education Program Adult Treatment Panel III guidelines (332) and the Joint Statement criteria (333). The hyperglycemia criteria in both definitions were considered to be fulfilled by all the included participants. The metabolic score (1-5) was calculated based on the number of criteria each participant fulfilled, and a score of three or more was considered to meet the criteria for the metabolic syndrome.

5.1.6 Definition of diabetic nephropathy and assessment of kidney function

Each participant collected timed urine samples for the measurement of the UAER. Each participant's kidney status was defined based on the UAER measured from at least two out of three consecutive overnight or 24-hour urine collections. A normal UAER was defined as < 20 μg/min or < 30 mg/24h, microalbuminuria as a UAER of ≥ 20 and < 200 μg/min or ≥ 30 and <3 00 mg/24h, and macroalbuminuria as a UAER of ≥ 200 μg/min or ≥ 300 mg/24h. Any participants undergoing dialysis treatment or having received a kidney transplant were considered to have end-stage renal disease. Diabetic nephropathy was defined as having either macroalbuminuria or end-stage renal disease. In some cases, a participant's renal status could not be classified due to there being too few urine collections or signs of non-diabetic renal disease.

The eGFR was calculated based on a single serum creatinine value using the CKD-EPI formula (80).

The CKD-EPI formula is calculated as follows:

Women

P-creatinine ≤ 62 µmol/l: $eGFR = 144 \times (creatinine/61.9)^{-0.329} \times (0.993)^{age}$

P-creatinine > 62 µmol/l: $eGFR = 144 \times (creatinine/61.9)^{-1.209} \times (0.993)^{age}$

Men

P-creatinine ≤ 80 µmol/l: $eGFR = 141 \times (creatinine/79.6)^{-0.411} \times (0.993)^{age}$

P-creatinine > 80 µmol/l: $eGFR = 141 \times (creatinine/79.6)^{-1.209} \times (0.993)^{age}$

The participants' kidney function was also grouped according to the stage of chronic kidney disease, as defined by the American National kidney Foundation Kidney Disease Outcome Quality Initiative guidelines (334) and based on the eGFR. Chronic kidney disease was divided into five stages as follows:

Stage 1 = eGFR of ≥ 90 ml/min/1.73m^2

Stage 2 = eGFR of ≥ 60-89 ml/min/1.73m^2

Stage 3 = eGFR of ≥ 30-59 ml/min/1.73m^2

Stage 4 = eGFR of ≥ 15-29 ml/min/1.73m^2

Stage 5 = eGFR of < 15 ml/min/1.73m^2 or dialysis treatment

5.1.7 Definition of diabetic retinopathy

Retinal laser photocoagulation was used as a marker of severe diabetic retinopathy. The accuracy of this approach has previously been validated, and approximately 80% of participants treated with laser photocoagulation were treated for proliferative retinopathy, while the remainder were treated for maculopathy or pre-proliferative retinopathy (335).

5.1.8 Definition of cardiovascular disease

Coronary heart disease was defined as a history of diagnosed myocardial infarction, coronary artery bypass surgery, coronary angioplasty, or treatment with long-acting nitroglycerin. A myocardial infarction was defined as a clinical event verified by the attending physician and the participant's medical records.

5.1.9 Medication

Lipid-lowering medication was defined as the use of statins, fibrates, and/or ezetimibe. Aspirin medication was defined as the use of low-dose acetylsalicylic acid (or clopidogrel) for the primary or secondary prevention of cardiovascular events. Warfarin medication was defined as the use of warfarin or any other anticoagulative medication, including new oral anticoagulants or low-molecular-weight heparins.

5.1.10 Definition of smoking

Current smoking was defined as smoking at least one cigarette per day for at least one year. A history of smoking was defined as current smoking, or smoking cessation prior to the data collection.

5.2 Laboratory measurements and assays

5.2.1 Lipids and lipoproteins

All the serum lipids and lipoproteins were measured from blood samples (non-fasting) in Professor Marja-Riitta Taskinen's research laboratory at Helsinki University Hospital, Department of Medicine, Division of Cardiology, Helsinki, Finland. The total cholesterol and triglycerides were measured enzymatically using a Cobas Mira analyzer (Hoffman-La Roche, Basel, Switzerland) with commercially available kits (Hoffman-La Roche until November 2001 and then ABX Diagnostics, HORIBA ABX, Montpellier, France until January 2006) and then by enzymatic determination using a Konelab 60i analyzer (Thermo Fisher Scientific Inc., Waltham, MA, USA) with kits obtained from the same manufacturer. The serum HDL-cholesterol was measured with an enzymatic colorimetric test using an HTS 7000 Plus Bio Assay Reader (Perkin Elmer, Waltham, MA, USA). The LDL-cholesterol was calculated using the Friedewald formula if the triglycerides were < 4.5 mmol/l (336):

LDL-cholesterol = Total cholesterol - HDL-cholesterol - (Triglycerides/2.2)

5.2.2 Glycemic control and insulin sensitivity

The HbA_{1c} was determined locally at each study center by means of standardized assays with a reference range of 4.0–6.0%. Since 2010, the reference range has been 20–42 mmol/mol. The insulin sensitivity was estimated with the estimated glucose disposal rate (eGDR), a formula derived from hyperinsulinemic euglycemic clamps (337). The formula was later modified for use with the HbA_{1c} (338). As another marker of insulin sensitivity, the total daily insulin dose divided by the body weight (IU/kg) was calculated.

$$eGDR = 24.4 - 12.97 \times WHR - 3.39 \times AHT - 0.60 \times HbA_{1c}$$

WHR = waist-to-hip ratio, AHT = antihypertensive treatment and/or blood pressure ≥ 140/90 mmHg (yes = 1, no = 0)

5.2.3 Creatinine

The serum creatinine was measured at a central laboratory by means of a kinetic Jaffe reaction using a Hitachi 911 E Analyzer (Boehringer Mannheim, Mannheim, Germany) until January 2002. After that, the creatinine was measured according to a photometric, enzymatic (isotope dilution mass spectrometry) method using a Hitachi 917 or Modular Analyzer (Boehringer Mannheim/Roche Diagnostics, Basel, Switzerland). The correlation coefficient between the two methods was 0.988.

A conversion formula was applied to enable the use of the results obtained via both methods:

$$S\text{-}Creatinine = (0.953 \times S\text{-}Creatinine\ Jaffe) - 7.261$$

5.2.4 Urinary albumin excretion rate

The urinary albumin excretion rate was determined from at least two out of three consecutive overnight or 24-hour urine collections at a central laboratory by means of radioimmunoassay using an LKB Wallac RIA Gamma Counter (Pharmacia, Uppsala, Sweden) until November 2002. After that, an immunoturbidimetric method was applied using a Hitachi 911 Analyzer (Roche Diagnostics, Hoffman-La Roche, Basel, Switzerland).

5.2.5 Definition of urinary salt excretion

The sodium and potassium intakes were estimated from the 24-hour urine collections and then expressed as the 24-hour urinary sodium excretion (24-h Na) and 24-hour urinary potassium excretion (24-h K) rates at a central laboratory using an indirect ion selective electrode. The sodium/potassium ratio (Na/K ratio) was defined as the 24-h Na divided by the 24-h K. Information concerning the 24-hour urinary sodium and potassium urinary excretion was available for 2,402 (59%) participants, of whom 115 (57%) had suffered an incident stroke.

5.2.6 High-sensitivity C-reactive protein

The high-sensitivity C-reactive protein was measured from the participants' blood serum in a central laboratory at Helsinki University Hospital using a photometric immunochemical method.

5.3 Stroke information about participants in Study III

In addition to the above-mentioned data, the data concerning the participants included in Study III included their HbA_{1c} values, creatinine concentrations, renal status, presence of coronary heart disease, medication, current smoking, age at stroke, and duration of diabetes at the time of the incident stroke. All this information was retrieved from medical records or death certificates at the time of the stroke. If no information was available from these sources, it was obtained from the FinnDiane visit closest to the time of the occurrence of the stroke.

5.4 Statistical analyses

All the variables included in the analyses were tested for the normal distribution. Normally distributed and continuous variables are presented as the mean ± standard deviation, while non-normally distributed continuous variables are presented as the median with the interquartile range. Any statistically significant differences between two groups of normally distributed variables were analyzed using Student's t-test. Any differences between the non-normally distributed variables for two groups was analyzed using the Mann-Whitney U-test. Any statistically significant differences between the categorical variables were tested using Pearson's χ^2-test. A p-value of < 0.05 was considered to be statistically significant in all the analyses.

5.4.1 Study I

The person-years of follow-up were calculated as the sum of the follow-up time in years for each included participant. The incidence of stroke, ischemic stroke, and hemorrhagic stroke are presented per 100,000 person-years, and adjusted for age. Separate Cox proportional hazards analyses were performed to examine how diabetic nephropathy and severe diabetic retinopathy affected the risk of stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke. The separate models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, BMI, LDL- and HDL-cholesterol, triglycerides, and history of smoking. The results are presented as the hazard ratio (HR) with a 95% confidence interval. The proportion of lacunar infarction among all the ischemic strokes across the groups of kidney status and severe diabetic nephropathy was calculated to assess the association between these diabetic complications and lacunar infarction. All the analyses were performed using SPSS statistical software version 19.0 (IBM Corporation, Armonk, NY, USA).

5.4.2 Study II

Cox proportional hazards analyses with forward stepwise variable entry and removal were performed to determine the independent risk factors for stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke, respectively. The variables that were associated with stroke in the univariate analyses were included in the multivariate analyses; therefore, the variables in the models for the different endpoints differed somewhat from each other. Some variables could not be tested in the same model due to collinearity. The main model for any type of stroke included the participants' sex, duration of diabetes, HbA_{1c}, waist circumference, diabetic nephropathy, severe diabetic retinopathy, systolic blood pressure, diastolic blood pressure, triglycerides, LDL-cholesterol, coronary heart disease, and history of smoking. Model 2 included the main model with the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure excluded, but with the eGDR included. Model 3 included the main model with the sex and duration of diabetes excluded, but with the eGFR included. Model 4 included the main model, but with the antihypertensive medication, lipid-lowering medication, and aspirin medication included.

The main model for ischemic stroke consisted of the participants' sex, duration of diabetes, waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, LDL- and HDL-cholesterol, HbA_{1c}, coronary heart disease, diabetic nephropathy, severe diabetic retinopathy, and history of smoking. In model 2, we included the main model and the eGDR, while we excluded the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure due

to collinearity. In model 3, in addition to the main model, we included the antihypertensive medication, lipid-lowering medication, and aspirin use.

In relation to lacunar infarction, similar models as used for ischemic stroke were built. The main model included the participants' sex, duration of diabetes, HbA_{1c}, waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, LDL- and HDL-cholesterol, coronary heart disease, diabetic nephropathy, severe diabetic retinopathy, and history of smoking. Model 2 included the main model with the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure excluded, but with the eGDR included. Model 3 included the main model with the antihypertensive medication, lipid-lowering medication, and aspirin medication included. Furthermore, model 4 included the main model with the participants' sex and duration of diabetes excluded, but with the eGFR included.

With regard to hemorrhagic stroke, the main model included the participants' sex, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure, triglycerides, diabetic nephropathy, severe diabetic retinopathy, and history of smoking. Model 2 included the main model with the antihypertensive medication, lipid-lowering medication, and aspirin medication included. Model 3 included the main model and the eGFR, while it excluded the participants' sex and duration of diabetes due to collinearity. The results of all the models and stroke subtypes are presented as the HR with a 95% confidence interval. All the analyses were performed with SPSS statistical software version 19.0 (IBM Corporation, Armonk, NY, USA).

5.4.3 Study III

We performed Cox proportional hazards analyses to study how the different blood pressure variables (i.e., systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure) affected the risk of total stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke. The results are presented as the HR with a 95% confidence interval. Due to collinearity, each blood pressure variable was included in separate models. Based on the results of the univariate analyses, the models were adjusted for sex, duration of diabetes, waist circumference, diabetic nephropathy, severe diabetic retinopathy, HbA_{1c}, LDL-cholesterol, current or history of smoking, and use of antihypertensive medication.

To assess the shapes of the associations between the continuous variables (i.e., systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure) and the risk of stroke, we fitted unadjusted Cox proportional hazards models with each variable included as a restricted cubic spline with three knots. The number of knots was selected based on the Akaike information criteria (339), and they were located at the 10^{th}, 50^{th}, and 90^{th} percentiles. The HR was estimated based on the restricted cubic spline models and then used to create

plots for the graphical assessment of the relationships. To determine whether the relationships between the blood pressure variables and the risk of stroke deviated from linearity, we implemented the Wald test. Similar restricted cubic spline models were built to evaluate the association between the 24-h Na, 24-h K, and Na/K ratio and the risk of stroke. The cubic spline analyses were performed with Harrell's Regression Modelling Strategies (rms) package (340) using R software (341). All the other analyses were performed with SPSS statistical software version 25.0 (IBM Corporation, Armonk, NY, USA).

5.4.4 Study IV

To estimate the participants' survival after the incident stroke, we produced Kaplan-Meier survival plots for overall survival, survival based on the ischemic or hemorrhagic stroke type, as well as survival based on the chronic kidney disease stage at the time of the stroke. To determine which factors independently predicted the participants' prognosis after an incident stroke, we performed Cox proportional hazards analyses. The analyses were based on the results of the univariate analyses of the statistical differences between the continuous and categorical variables, or on the survival analyses. We adjusted the analyses for the incident stroke type (ischemic or hemorrhagic stroke), kidney status, and lacunar infarction. The results are presented as the HR with a 95% confidence interval. All the analyses were performed using the SPSS statistical software version 23.0 (IBM Corporation, Armonk, NY, USA).

6 RESULTS

6.1 Incidence of stroke and its subtypes in people with type 1 diabetes (Study I)

The mean follow-up period for Study I was 9.0 ± 2.7 years, and the total person-years of follow-up was 36,680. Of the 149 participants who suffered an incident stroke, 105 (70%) suffered ischemic strokes and 44 (30%) suffered hemorrhagic strokes. Of the ischemic strokes, 58 (55%) were lacunar infarctions. Of all the strokes, 20 were fatal, 4 (4%) ischemic strokes and 16 (36%) hemorrhagic strokes, as shown in Table 4. The proportions of the microvascular diabetic complications in the participants who did not suffer a stroke when compared with those who suffered ischemic stroke, lacunar infarction, and hemorrhagic stroke are shown in Table 5. Those who suffered any type of stroke were older and had a longer duration of diabetes. The presence of both diabetic nephropathy and severe diabetic retinopathy was more common at baseline in those who suffered any type of stroke. The majority of participants who suffered a stroke of any subtype had both severe diabetic retinopathy and diabetic nephropathy when considering the combined variable for those two microvascular complications (Table 5).

TABLE 5. Proportion of diabetic microvascular complications in participants who suffered no stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke during the follow-up period

BASELINE DATA **n**	**No stroke** **3,934**	**Ischemic stroke** **105**	**Lacunar infarction** **58**	**Hemorrhagic stroke** **44**
Men (%)	51	66*	69*	64
Age (years)	37.1 ± 11.8	46.1 ± 9.8*	45.1 ± 8.8*	44.0 ± 8.1*
Age at onset (years)	15.8 ± 9.0	15.3 ± 9.6	14.6 ± 9.2	14.4 ± 8.8
Duration of diabetes (years)	21.3 ± 12.1	30.8 ± 9.0*	30.5 ± 8.7*	29.6 ± 8.1*
Kidney status				
Normal UAER	2,455 (62%)	19 (18%)*	10 (17%)*	8 (18%)*
Microalbuminuria	486 (12%)	18 (17%)	12 (21%)*	6 (14%)
Macroalbuminuria	499 (13%)	42 (40%)*	24 (41%)*	8 (18%)*
ESRD	241 (6%)	26 (25%)*	12 (21%)*	22 (50%)*
Microvascular complications				
DN	740 (19%)	68 (65%)*	36 (62%)*	30 (68%)*
SDR	1,260 (32%)	80 (76%)*	44 (76%)*	35 (80%)*
Combined DN and SDR				
Neither complication	2,392 (65%)	15 (14%)*	10 (17%)*	6 (14%)*
Only SDR	549 (15%)	22 (21%)	12 (21%)	7 (16%)
Only DN	112 (3%)	10 (10%)*	4 (7%)	2 (5%)
Both SDR and DN	634 (17%)	58 (55%)*	32 (55%)*	28 (65%)*

The data are presented as the mean ± standard deviation or number of cases (%). * = $p < 0.05$ when compared with no stroke at follow-up. UAER = urinary albumin excretion rate, ESRD = end-stage renal disease, DN = diabetic nephropathy, SDR = severe diabetic retinopathy.

The incidence of any type of stroke stratified by sex is shown in Figure 5A (Hägg-Holmberg *et al*, previously unpublished data). The incidence of ischemic stroke and hemorrhagic stroke in each age group are shown in Figure 5B (Hägg-Holmberg *et al*, previously unpublished data). The incidence of any type of stroke was higher in the male participants across all the age groups. The highest incidence of ischemic stroke was found in those aged 60–69 years at baseline, while no one over 70 years old suffered a hemorrhagic stroke. As shown in Figure 5B, the incidence of ischemic stroke was higher than the incidence of hemorrhagic stroke. Further, the youngest participants who suffered a stroke were under the age of 30 and suffered from a stroke of the ischemic subtype. The total incidence rates for each type of stroke are shown in Table 6.

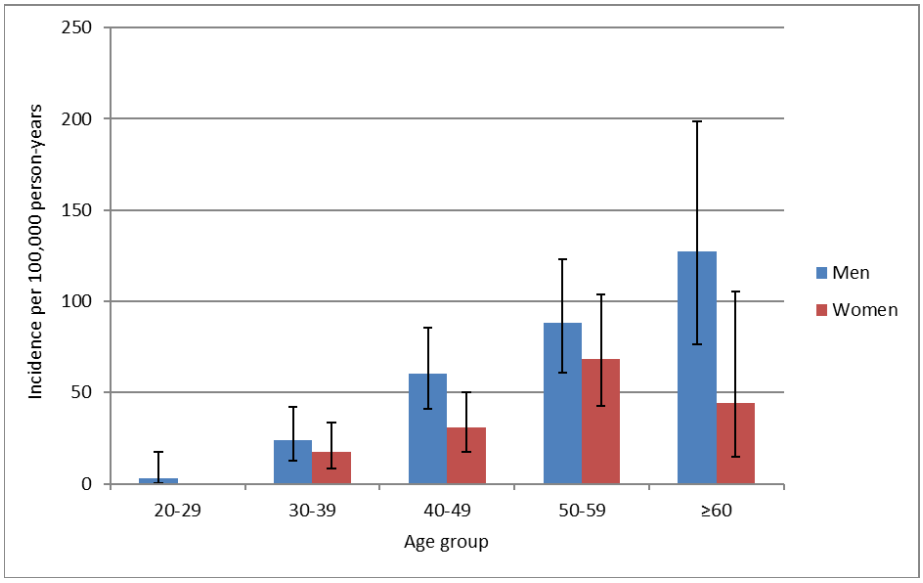

Figure 5A. Incidence per 100,000 person-years of any type of stroke according to sex and age group. Men are depicted in blue, women in red.

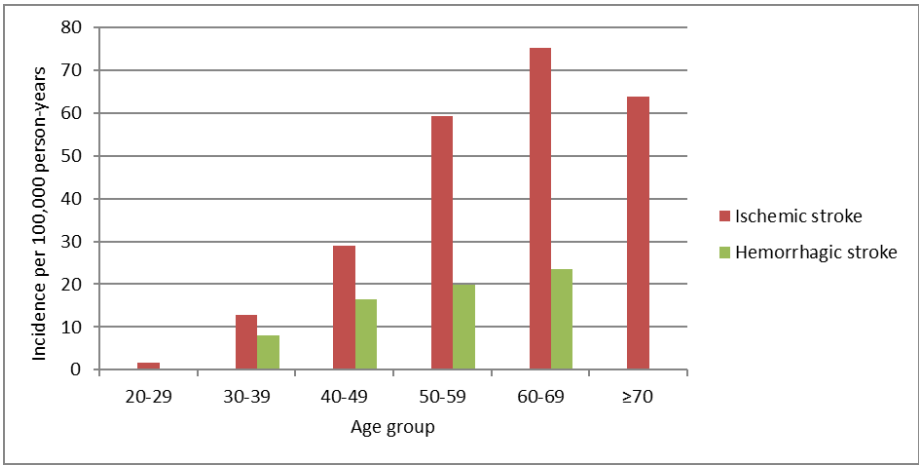

Figure 5B. Incidence of ischemic stroke (red) and hemorrhagic stroke (green) according to age.

The incidence of stroke of any subtype, ischemic stroke, lacunar infarction, and hemorrhagic stroke according to the presence of diabetic nephropathy and retinopathy are shown in Table 6. The incidence was found to increase with advancing diabetic nephropathy, and for all the subtypes of stroke, the incidence was the highest in those individuals with end-stage renal disease. Furthermore, the incidence of any subtype of stroke was multifold in those with diabetic retinopathy when compared with the incidence if no retinopathy was present (Table 6).

TABLE 6. Incidence of any stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke according to the presence of diabetic nephropathy and severe diabetic retinopathy

	Any stroke	Ischemic stroke	Lacunar infarction	Hemorrhagic stroke
Total incidence	406 (344–477)	286 (234–347)	158 (120–204)	120 (87–161)
DN				
Normal UAER	122 (81–178)	86 (52–135)	45 (22–83)	36 (16–71)
Microalbuminuria	501 (321–745)	376 (223–594)	250 (129–437)	125 (46–273)
Macroalbuminuria	928 (689–1,223)	779 (562–1,053)	445 (285–663)	148 (64–292)
ESRD	1,959 (1,444–2,597)	1,061 (693–1,555)	490 (253–855)	898 (563–1,359)
SDR				
No retinopathy	141 (98–198)	104 (67–154)	58 (32–98)	37 (17–71)
Retinopathy	909 (751–1,091)	632 (501–787)	348 (253–467)	277 (193–385)

The data are presented as the incidence per 100,000 person-years of follow-up with a 95% confidence interval. DN = diabetic nephropathy, UAER = urinary albumin excretion rate, SDR = severe diabetic retinopathy.

As the incidence increased with the presence of diabetic complications, we sought to explore how the microvascular diabetic complications of interest, namely diabetic nephropathy and severe diabetic retinopathy, independently affected the risk of stroke and its subtypes. For each subgroup, we performed Cox proportional hazards analyses. The results of the analyses are presented in Table 7. The risk was found to be similar to that of the incidence for each complication and each subtype. The risk of stroke increased with each stage of diabetic nephropathy, and the presence of severe diabetic retinopathy increased the risk for all the stroke subtypes. The highest risk was seen in those with end-stage renal disease, especially those who suffered a hemorrhagic stroke.

TABLE 7. Cox regression analyses for any stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke according to the presence of diabetic nephropathy and severe diabetic retinopathy

	Any stroke	Ischemic stroke	Lacunar infarction	Hemorrhagic stroke
DN				
Normal UAER	1.0	1.0	1.0	1.0
Microalbuminuria	3.2 (1.9–5.6)	3.3 (1.7–6.3)	4.3 (1.8–10.0)	3.2 (1.1–9.3)
Macroalbuminuria	4.9 (2.9–8.2)	5.2 (2.9–9.6)	5.7 (2.5–12.9)	3.6 (1.2–10.5)
ESRD	7.5 (4.2–13.3)	5.5 (2.7–11.3)	5.1 (1.9–14.1)	14.9 (5.5–40.9)
SDR				
No retinopathy	1.0	1.0	1.0	1.0
Retinopathy	3.0 (1.9–4.5)	2.7 (1.6–4.4)	2.8 (1.5–5.5)	3.9 (1.7–8.9)
Combined DN and SDR				
Neither complication	1.0	1.0	1.0	1.0
Only SDR	3.3 (1.8–5.8)	3.4 (1.7–6.6)	2.9 (1.2–6.9)	3.0 (1.0–8.9)
Only DN	7.2 (3.5–15.1)	7.9 (3.4–18.2)	5.0 (1.5–16.6)	5.3 (1.1–26.9)
Both complications	6.1 (3.6–10.3)	5.7 (3.0–10.9)	5.0 (2.2–11.3)	7.4 (2.8–19.3)

The data are presented as the hazard ratio with a 95% confidence interval. The analyses also included age, sex, systolic blood pressure, diastolic blood pressure, BMI, LDL- and HDL-cholesterol, triglycerides, and history of smoking. The reference groups were normal UAER, no SDR, and neither complications in the separate analyses. DN = diabetic nephropathy, UAER = urinary albumin excretion rate, ESRD = end-stage renal disease, SDR = severe diabetic retinopathy.

To further study the association between lacunar infarction and the microvascular complications, we assessed the proportion of lacunar infarctions among the total number of infarctions across the diabetic nephropathy and severe diabetic retinopathy groups as well as in relation to the combined variable. The results for the latter variable are shown in Figure 6. The proportion of lacunar infarctions among the total number of infarctions was similar in those with normal UAER, microalbuminuria, macroalbuminuria, end-stage renal disease, and severe diabetic retinopathy. We did not identify any association with lacunar infarction or the microvascular complications in any of the groups.

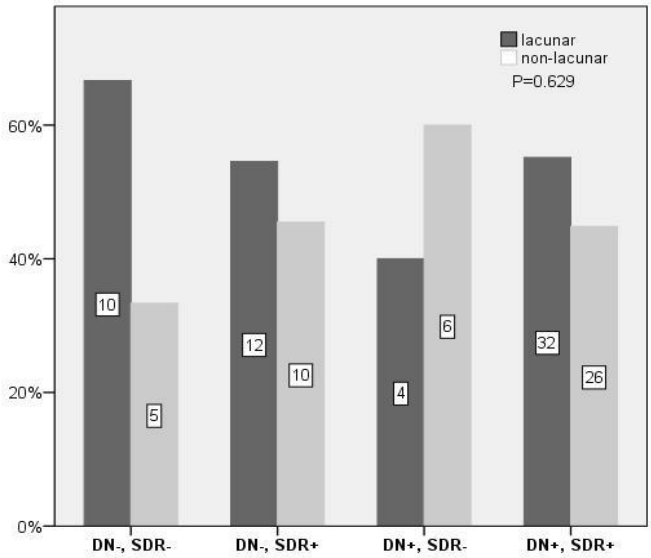

FIGURE 6. Proportion of lacunar and non-lacunar infarction among the total infarctions (i.e., ischemic strokes) in participants with neither complication, only severe diabetic retinopathy, only diabetic nephropathy, or both complications. The numbers in the bars represent the number of participants in each group. Copyright © 2013 American Diabetes Association from Diabetes Care®, Vol.36;4140-4146. Reprinted with permission from the American Diabetes Association.

6.2 Independent risk factors for stroke and its subtypes (Study II)

Table 8 presents the clinical characteristics of the included participants, as based on the type of incident stroke they suffered when compared with those who suffered no stroke. The participants who suffered non-lacunar infarction and lacunar infarction were older, had a longer duration of diabetes, had a higher waist circumference, had a higher total cholesterol and triglycerides, and a higher proportion used lipid-lowering medication when compared with those who did not suffer a stroke. They also had lower insulin sensitivity, poorer glycemic control, and higher systolic and diastolic blood pressure, and they had more commonly been treated with antihypertensive medication and aspirin. Diabetic microvascular complications, coronary heart disease, the metabolic syndrome, and a history of smoking were all more common in these participants, while no differences were seen in relation to the age at the onset of diabetes, use of warfarin medication, or current smoking.

Hemorrhagic stroke, however, differed from the other stroke types in that there were no significant differences in the proportions of men, age, waist circumference, glycemic control, the metabolic syndrome, coronary heart disease, current smoking, or history of smoking. In contrast, the BMI was significantly lower in those who suffered a stroke of the hemorrhagic subtype when compared with those who did not suffer a stroke.

TABLE 8. Baseline characteristics of the participants included in Studies I, II, and IV with no stroke, non-lacunar infarction, lacunar infarction, and hemorrhagic stroke during the follow-up period

BASELINE DATA	No stroke	Any stroke	Non-lacunar infarction	Lacunar infarction	Hemorrhagic stroke
n	**3,934**	**149**	**47**	**58**	**44**
Men (%)	51	65*	62	69*	64
Age (years)	37.1 ± 11.8	45.5 ± 9.3*	47.3 ± 10.8*	45.1 ± 8.8*	44.0 ± 8.1*
Age at onset of diabetes (years)	15.8 ± 9.0	15.0 ± 9.3	16.2 ± 10.0	14.6 ± 9.2	14.4 ± 8.8
Duration of diabetes (years)	21.0 (11.0–30.0)	31.0 (24.0–36.0)*	34.0 (25.0–41.0)*	31.5 (24.0–36.0)*	29.0 (24.0–35.5)*
Age at stroke (years)	-	50.5 ± 9.1	50.5.1 ± 9.1	50.3 ± 8.9	48.7 ± 7.7
BMI (kg/m^2)	25.0 ± 3.6	24.9 ± 3.7	25.1 ± 3.8	25.5 ± 3.9	23.9 ± 3.2*
Waist circumference (cm)	84.0 (77.0–92.0)	88.0 (80.0–97.0)*	91.0 (86.0–100.0)*	88.0 (80.3–97.8)*	86.0 (78.5–92.5)
Systolic blood pressure (mmHg)	133 ± 18	151 ± 24*	154 ± 25*	151 ± 22*	148 ± 25*
Diastolic blood pressure (mmHg)	79 ± 10	84 ± 12*	85 ± 10*	84 ± 12*	84 ± 12*
hs-C-reactive protein (mg/l)	1.77 (1.07–3.22)	2.19 (1.25–3.86)*	2.43 (1.69–6.69)*	2.29 (1.21–3.89)	1.99 (1.16–2.98)
Lipids and lipoproteins					
Total cholesterol (mmol/l)	4.9 ± 1.0	5.3 ± 1.1*	5.5 ± 1.3*	5.2 ± 0.9*	5.4 ± 1.3*
LDL cholesterol (mmol/l)	3.0 ± 0.9	3.4 ± 1.0*	3.5 ± 1.2*	3.4 ± 0.8*	3.3 ± 1.1
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	1.2 ±0.3*	1.3 ± 0.4
Triglycerides (mmol/l)	1.02 (0.77–1.46)	1.30 (0.96–1.71)*	1.21 (0.90–1.80)*	1.30 (1.05–1.62)*	1.32 (0.92–1.88)*
Glycemic control and insulin sensitivity					
HbA_{1c} (%)	8.4 ± 1.5	8.9 ± 1.3*	9.1 ± 1.5*	8.9 ± 1.1*	8.7 ± 1.3
eGDR (mg/kg/min)	6.23 (4.39–8.55)	4.13 (2.95–5.19)*	3.94 (2.68–4.82)*	3.89 (2.98–4.89)*	4.44 (2.94–5.80)*
Metabolic syndrome NCEP/JS (%)	33/48	53*/66*	54*/67*	56*/70*	46/61
Micro- and macrovascular complications					
eGFR (ml/min/1.73m^2)	101 (82–115)	65 (36–98)*	62 (39–91)*	66 (42–98)*	60 (31–100)*
Diabetic nephropathy (%)	20	66*	68*	62*	68*
Severe diabetic retinopathy (%)	32	77*	77*	76*	80*
Coronary heart disease (%)	5	15*	19*	18*	7
Medication and smoking					
Anti-hypertensive medication (%)	36	82*	85*	81*	82*
Lipid-lowering medication (%)	11	25*	27*	21*	30*
Aspirin (%)	12	31*	38*	26*	32*
Warfarin (%)	1	1	2	0	0
Current smoking (%)	24	29	23	33	32
History of smoking (%)	46	63*	71*	62*	56

The data are presented as the mean ± standard deviation, median with interquartile range, or number of cases (%). * = $p < 0.05$ when compared with no stroke. BMI = body mass index, hs-C-reactive protein = high-sensitivity C-reactive protein, eGDR = estimated glucose disposal rate, NCEP = National Cholesterol Education Program Adult Treatment Panel III criteria, JS = Joint Statement criteria, eGFR = estimated glomerular filtration rate.

We performed Cox proportional hazards analyses for the different stroke types in order to assess the independent risk factors for each group. The variables included in the different models are discussed in section 5.4.2. The risk factors for stroke of any type are shown in Table 9. The independent risk factors were higher systolic blood pressure, a longer duration of diabetes, the presence of diabetic nephropathy or severe diabetic retinopathy, higher HbA_{1c}, and a history of smoking. In the separate model that included the eGDR, a lower eGDR was found to be independently associated with an increased risk of stroke. The same was seen for eGFR, while the use of antihypertensive medication also independently increased the risk of any type of stroke (Table 9).

TABLE 9. Independent risk factors for any stroke type

	Main model	**p**
SBP (mmHg)	1.02 (1.01–1.03)	< 0.001
Duration of diabetes (years)	1.04 (1.02–1.06)	< 0.001
DN (yes/no)	2.28 (1.46–3.54)	< 0.001
HbA_{1c} (%)	1.17 (1.04–1.32)	0.010
SDR (yes/no)	1.90 (1.15–3.13)	0.012
History of smoking (yes/no)	1.58 (1.10–2.29)	0.015
	Model 2	p
Duration of diabetes (years)	1.04 (1.02–1.06)	< 0.001
DN (yes/no)	2.30 (1.49–3.55)	< 0.001
SDR (yes/no)	1.80 (1.09–2.99)	0.022
History of smoking (yes/no)	1.50 (1.04–2.16)	0.031
eGDR (mg/kg/min)	0.83 (0.75–0.92)	< 0.001
	Model 3	p
SBP (mmHg)	1.02 (1.01–1.03)	< 0.001
HbA_{1c} (%)	1.15 (1.02–1.30)	0.020
SDR (yes/no)	2.74 (1.70–4.41)	< 0.001
eGFR (ml/min/1.73m^2)	0.99 (0.98–0.99)	< 0.001
	Model 4	p
SBP (mmHg)	1.02 (1.01–1.03)	< 0.001
Duration of diabetes (years)	1.04 (1.02–1.06)	< 0.001
DN (yes/no)	1.73 (1.09–2.74)	0.020
HbA_{1c} (%)	1.16 (1.03–1.31)	0.016
SDR (yes/no)	1.65 (1.09–2.71)	0.046
History of smoking (yes/no)	1.56 (1.07–2.25)	0.019
AHT medication (yes/no)	2.18 (1.25–3.78)	0.006

The data are presented as the hazard ratio with a 95% confidence interval. SBP = systolic blood pressure, DN = diabetic nephropathy, SDR = severe diabetic retinopathy, eGDR = estimated glucose disposal rate, eGFR = estimated glomerular filtration rate, AHT medication = antihypertensive medication.

The main model also included the participants' sex, waist circumference, diastolic blood pressure, triglycerides, LDL-cholesterol, and coronary heart disease. Model 2 included the main model with the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure excluded, but with the eGDR included. Model 3 included the main model with the sex and duration of diabetes excluded, but with the eGFR included. Model 4 included the main model with the AHT medication, lipid-lowering medication, and aspirin medication included.

The risk factor profiles for ischemic stroke and lacunar infarction were similar to the profile for any type of stroke. The results of the different models are shown in Table 10. The variables in the different models for the stroke subtypes are discussed in section 5.4.2. In terms of ischemic stroke, severe diabetic retinopathy did not prove to be an independent risk factor in any of the models. Similar risk factors as for ischemic stroke was seen for lacunar infarction. However, a history of smoking was not a risk factor for that subtype. In addition, in the model that included the eGFR, both severe diabetic retinopathy and a lower eGFR proved to be independently associated with lacunar infarction. The participants' sex, waist circumference, triglycerides, LDL- and HDL-cholesterol, diastolic blood pressure, coronary heart disease, lipid-lowering medication, and aspirin medication were not significant in any of the models for either ischemic stroke or lacunar infarction.

The risk factor profile for hemorrhagic stroke differed from the profiles for the other stroke subtypes, as shown in Table 10. The variables in the different models for hemorrhagic stroke are discussed in section 5.4.2. The independent risk factors for hemorrhagic stroke were found to be a lower BMI, a higher systolic blood pressure, diabetic nephropathy, and severe diabetic retinopathy. In separate models, a lower eGFR and lipid-lowering medication were also found to be associated with an increased risk of hemorrhagic stroke. The duration of diabetes, diastolic blood pressure, triglycerides, and history of smoking were not associated with hemorrhagic stroke, and nor were the eGDR, antihypertensive medication, and aspirin medication.

TABLE 10. Risk factors for the stroke subtypes

	Ischemic stroke		Lacunar infarction		Hemorrhagic stroke	
	Main model	**p**	**Main model**	**p**	**Main model**	**p**
Duration of diabetes (years)	1.06 (1.04–1.08)	< 0.001	1.05 (1.02–1.08)	< 0.001	-	-
DN (yes/no)	2.81 (1.75–4.51)	< 0.001	2.72 (1.45–5.10)	0.002	2.77 (1.20–6.42)	0.017
SBP (mmHg)	1.02 (1.01–1.03)	< 0.001	1.02 (1.00–1.03)	0.013	1.02 (1.00–1.03)	0.019
History of smoking (yes/no)	1.93 (1.23–3.02)	0.004	-	-	-	-
HbA_{1c} (%)	1.23 (1.06–1.41)	0.005	1.22 (1.01–1.47)	0.042	NA	NA
BMI (kg/m^2)	NA	NA	NA	NA	0.89 (0.81–0.98)	0.016
SDR (yes/no)	-	-	-	-	2.99 (1.18–7.55)	0.021
	Model 2	p	Model 2	p		
Duration of diabetes (years)	1.06 (1.03–1.08)	< 0.001	1.05 (1.02–1.08)	0.001		
DN (yes/no)	2.56 (1.59–4.13)	< 0.001	2.26 (1.21–4.24)	0.011		
History of smoking (yes/no)	1.74 (1.12–2.72)	0.014	-	-		
eGDR (mg/kg/min)	0.78 (0.69–0.88)	< 0.001	0.76 (0.65–0.88)	< 0.001		
	Model 3	p	Model 3	p	Model 2	p
Duration of diabetes (years)	1.05 (1.03–1.08)	< 0.001	1.04 (1.01–1.07)	0.007	-	-
DN (yes/no)	1.89 (1.13–3.16)	0.015	-	-	2.49 (1.06–5.81)	0.036
SBP (mmHg)	1.02 (1.01–1.03)	0.001	1.02 (1.00–1.03)	0.036	1.02 (1.00–1.03)	0.036
History of smoking (yes/no)	1.91 (1.21–3.00)	0.005	-	-	-	-
HbA_{1c} (%)	1.21 (1.05–1.40)	0.008	-	-	NA	NA
AHT medication (yes/no)	2.53 (1.31–4.89)	0.006	2.99 (1.27–7.07)	0.013	-	-
BMI (kg/m^2)	NA	NA	NA	NA	0.88 (0.80–0.97)	0.008
SDR (yes/no)	-	-	-	-	2.89 (1.14–7.30)	0.025
Lipid-lowering medication (yes/no)	-	-	-	-	2.38 (1.14–4.74)	0.021
			Model 4	p	Model 3	p
SBP (mmHg)			1.02 (1.01–1.03)	0.006	1.02 (1.00–1.03)	0.027
SDR (yes/no)			2.89 (1.37–6.08)	0.005	3.18 (1.29–7.82)	0.012
eGFR ($ml/min/1.73m^2$)			0.99 (0.98–0.99)	0.007	0.99 (0.98–0.99)	0.004
BMI (kg/m^2)			NA	NA	0.88 (0.80–0.97)	0.012

The data are presented as the hazard ratio with a 95% confidence interval. The main model for ischemic stroke also included sex, waist circumference, diastolic blood pressure, triglycerides, LDL- and HDL-cholesterol, and coronary heart disease. Model 2 = main model with the estimated glucose disposal rate included, but with the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure excluded. Model 3 = main model with the antihypertensive medication, lipid-lowering medication, and aspirin medication included. The main model for lacunar infarction included sex, waist circumference, diastolic blood pressure, triglycerides, LDL- and HDL-cholesterol, and coronary heart disease. Model 2 = main model with the HbA_{1c}, waist circumference, systolic blood pressure, and diastolic blood pressure excluded, but with the estimated glucose disposal rate included. Model 3 = main model with the antihypertensive medication, lipid-lowering medication, and aspirin medication included. Model 4 = main model with the sex and duration of diabetes excluded, but with the estimated glomerular filtration rate included. The main model for hemorrhagic stroke included sex, diastolic blood pressure, and triglycerides. Model 2 = main model with the AHT medication, lipid-lowering medication, and aspirin medication included. Model 3 = main model with the estimated glomerular filtration rate included, but with the sex and duration of diabetes excluded. DN = diabetic nephropathy, SBP = systolic blood pressure, BMI = body mass index, SDR = severe diabetic retinopathy, eGDR = estimated glucose disposal rate, AHT medication = antihypertensive medication, eGFR = estimated glomerular filtration rate. NA = not applicable in the model in question. The hazard ratios with corresponding p-values are only presented for those variables that were significant in the multivariate analyses.

As diabetic nephropathy proved to be a strong risk factor for stroke, we performed Cox proportional hazards analyses in only those participants with normal UAER in an attempt to eliminate the effect of diabetic nephropathy. Table 11 displays the results of those analyses (Hägg-Holmberg *et al*, previously unpublished data). The male sex, a longer duration of diabetes, severe diabetic retinopathy, and coronary heart disease were all independent risk factors for any type of stroke in the participants with normal UAER.

TABLE 11. Independent risk factors for any type of stroke in participants with a normal albumin excretion rate

	Main model	**p**
Sex (male)	2.79 (1.20–6.44)	0.017
Duration (years)	1.04 (1.01–1.08)	0.026
CHD (yes/no)	3.54 (1.24–10.1)	0.018
SDR (yes/no)	3.09 (1.28–7.49)	0.012
	Model 2	p
CHD (yes/no)	5.35 (1.93–14.9)	0.001
SDR (yes/no)	6.39 (2.81–14.6)	< 0.001
	Model 3	p
CHD (yes/no)	5.14 (1.86–14.2)	0.002
SDR (yes/no)	5.65 (2.53–12.6)	< 0.001
	Model 4	p
CHD (yes/no)	3.54 (1.24–10.1)	0.018
SDR (yes/no)	3.08 (1.27–7.46)	0.013
Sex (male)	2.78 (1.20–6.44)	0.017
Duration of diabetes (years)	1.04 (1.01–1.08)	0.026

The data are presented as the hazard ratio with a 95% confidence interval. The main model included sex, duration of diabetes, coronary heart disease, severe diabetic retinopathy, and history of smoking. Model 2 = main model with the estimated glucose disposal rate included. Model 3 = main model with the sex and duration of diabetes excluded, but with the estimated glomerular filtration rate included. Model 4 = main model with the antihypertensive medication, lipid-lowering medication, and aspirin medication included. CHD = coronary heart disease, SDR = severe diabetic retinopathy.

6.3 Effect of blood pressure and urinary salt excretion on the risk of stroke (Study III)

The participants in Study III included an additional 53 new incident stroke cases when compared with the participants in Studies I and II. This resulted in a total of 202 incident stroke cases by the end of 2012. Among them, 145 (72%) were ischemic strokes and 57 (28%) were hemorrhagic strokes. Of the ischemic strokes, 70 (48%) were non-lacunar infarctions and 75 (52%) were lacunar infarctions. The baseline characteristics of the participants are shown in Table 12.

TABLE 12. Clinical characteristics according to the blood pressure variables and antihypertensive medication of participants with no stroke and any type of stroke during the follow-up period

BASELINE DATA	No Stroke	Any Stroke
n	3,903	202
Blood pressure and urinary salt excretion		
SBP (mmHg)	133 ± 18	150 ± 23*
DBP (mmHg)	79 ± 10	83 ± 11*
MAP (mmHg)	97 ± 11	105 ± 13
PP (mmHg)	54 ± 16	67 ± 19*
Hypertensive (%)	32	66*
24-h Na (mmol/l)	140 (101–185)	145 (98–192)
24-h K (mmol/l)	83 (62–105)	79 (59–104)
Na/K ratio	1.74 (1.32–2.30)	1.76 (1.45–2.33)
Antihypertensive medication		
Any type of AHT medication (%)	36	78*
- ACE inhibitor (%)	24	45*
- Angiotensin receptor blocker (%)	5	12*
- Calcium channel blocker (%)	11	33*
- β blocker (%)	12	38*
- Diuretic (%)	11	36*
- Other (%)	1	2*

The data are presented as the mean ± standard deviation, median with interquartile range, or number of cases (%). * = $p < 0.05$ when compared with no stroke. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, 24-h Na = 24-hour urinary sodium excretion, 24-h K = 24-hour urinary potassium excretion, Na/K ratio = sodium/potassium ratio, AHT-medication = antihypertensive medication, ACE inhibitor = angiotensin-converting enzyme inhibitor.

All the blood pressure variables except for the mean arterial pressure were higher in the participants who had suffered a stroke, and the majority of those who had suffered a stroke were hypertensive. No differences in the sodium or potassium intake (expressed as the urinary excretion) were identified. Almost 80% of the participants who had suffered a stroke used antihypertensive medication. More specifically, angiotensin-converting enzyme inhibitors were used by 45% of participants who had suffered a stroke, angiotensin receptor blockers by 12%, calcium channel blockers by 33%, β blockers by 38%, and diuretics by 36% (Table 12).

To determine how the different blood pressure variables independently affected the risk of stroke, we performed Cox proportional hazards analyses adjusted for the participants' sex, waist circumference, duration of diabetes, diabetic nephropathy, HbA_{1c}, LDL-cholesterol, severe diabetic retinopathy, current or history of smoking, and antihypertensive medication use. The different blood pressure variables were included in separate models due to collinearity. The results of the analyses are presented in Table 13.

TABLE 13. Blood pressure as a risk factor for any stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke

	Any stroke	Ischemic stroke	Lacunar infarction	Hemorrhagic stroke
SBP	1.20 (1.11–1.29)*	1.20 (1.10–1.30)*	1.16 (1.03–1.32)*	1.21 (1.05–1.40)*
DBP	1.21 (1.03–1.41)*	1.15 (0.95–1.38)	1.09 (0.84–1.40)	1.38 (1.02–1.88)*
MAP	1.32 (1.15–1.51)*	1.29 (1.10–1.51)*	1.21 (0.97–1.52)	1.42 (1.10–1.85)*
PP	1.20 (1.10–1.31)*	1.21 (1.10–1.34)*	1.18 (1.03–1.37)*	1.16 (0.98–1.38)

The data are presented as the hazard ratio with a 95% confidence interval. The hazard ratio is given per 10 mmHg increase for each blood pressure variable. The model also included the participants' sex, waist circumference, diabetes duration, diabetic nephropathy, HbA_{1c}, LDL-cholesterol, severe diabetic retinopathy, any smoking, and antihypertensive medication. The different blood pressure variables were included in separate models. * = $p < 0.05$. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure.

All the different blood pressure variables were independently associated with an increased risk of any type of stroke, while the systolic blood pressure, mean arterial pressure, and pulse pressure were independently associated with an increased risk of ischemic stroke. In terms of lacunar infarction, only the systolic blood pressure and pulse pressure increased the risk of that particular stroke subtype. With regard to hemorrhagic stroke, all the blood pressure variables except for the pulse pressure were independently associated with an increased risk.

To further clarify which of the blood pressure variables had the strongest association with the risk of stroke, we included all the different variables in the same model in turn. The systolic blood pressure remained significant for any stroke, ischemic stroke, and lacunar infarction, while the association with the other blood pressure variables was insignificant. In the case of hemorrhagic stroke, only the mean arterial pressure remained significant in the model (data not shown).

To determine how the different blood pressure variables affected the risk of stroke, as well as to investigate the blood pressure levels at which the risk of stroke started to increase, we performed restricted cubic splines of the Cox proportional hazards models. Linearity was not assumed in any of the analyses. Moreover, all the models were unadjusted. Figure 7A-D show the estimated HRs for any stroke and the different blood pressure variables. The p-value for non-linearity was significant for the pulse pressure and diastolic blood pressure, but not for the systolic blood pressure or mean arterial pressure. However, only values at the higher end were found to increase the risk of stroke, and no J-shaped association was seen for any of the variables. The risk of stroke began to increase when the systolic blood pressure exceeded 131 mm Hg, when the diastolic blood pressure exceeded 80 mmHg, when the mean arterial pressure exceeded 97 mmHg, or when the pulse pressure exceeded 52 mmHg.

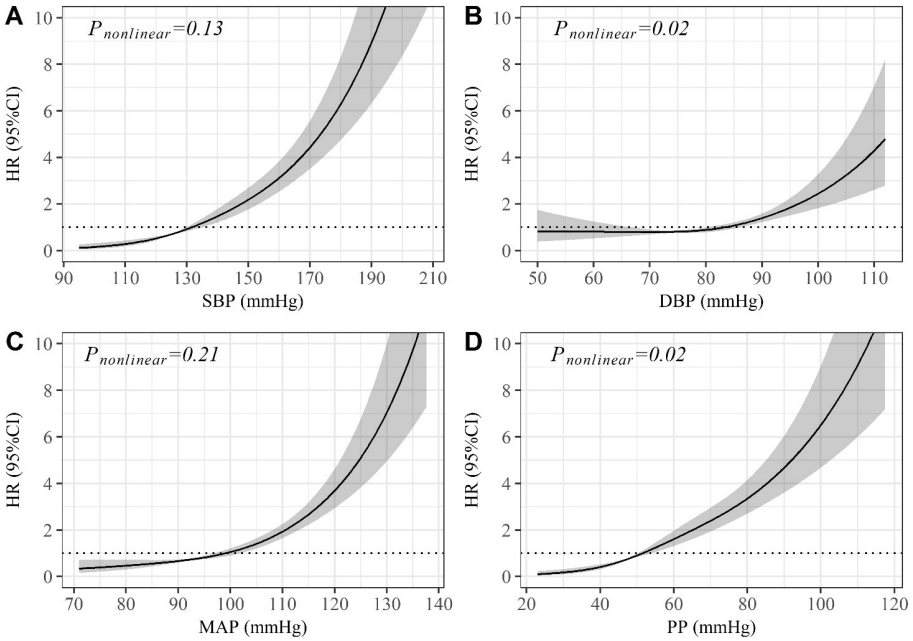

FIGURE 7. Restricted cubic spline model for any stroke and the SBP, DBP, MAP, and PP. The risk of any stoke in relation to (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), (C) mean arterial pressure (MAP), and (D) pulse pressure (PP), as estimated using restricted cubic splines models with three knots. The unadjusted hazard ratios (HRs) are represented by the solid line and the 95% confidence interval (CI) by the shaded area. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure. Previously published in 2019 in Cardiovascular Diabetology, 18:88. Reprinted with the permission of the copyright holders.

In separate analyses concerning ischemic and hemorrhagic stroke and the blood pressure variables, similar results were obtained as were seen for any type of stroke (Figure 8A-D). The risk of both subtypes began to increase when the systolic blood pressure was > 130 mmHg as well as when the diastolic blood pressure exceeded 80 mmHg. The p-value for non-linearity was significant for the diastolic blood pressure and hemorrhagic stroke as well as for the pulse pressure and ischemic stroke. However, no J-shaped association was seen for either subtype, nor was there any trend toward a higher risk of the two stroke subtypes at the lower end of the blood pressure values.

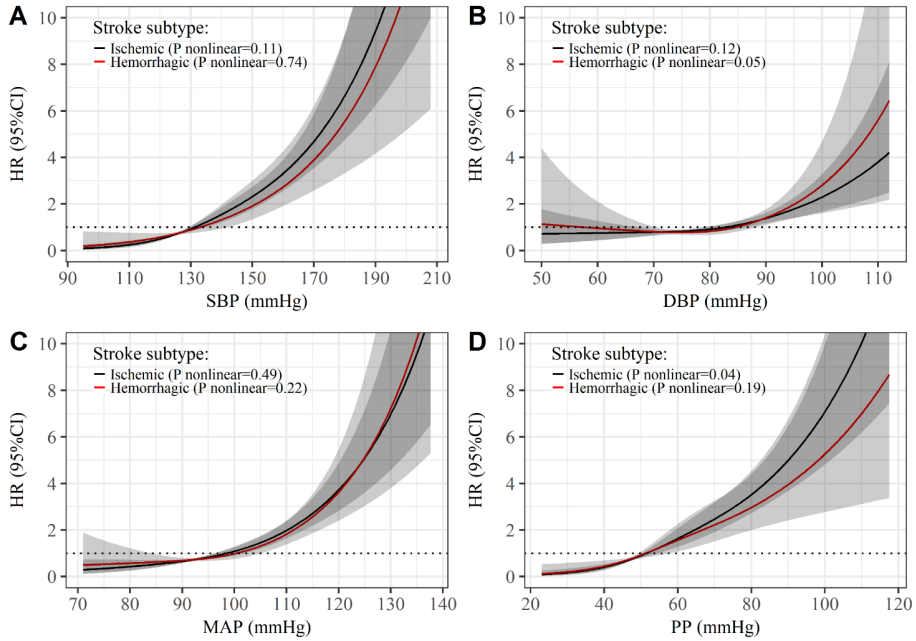

FIGURE 8. Restricted cubic spline models for ischemic and hemorrhagic stroke and the SBP, DBP, MAP, and PP. The risk of ischemic and hemorrhagic stroke in relation to (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), (C) mean arterial pressure (MAP), and (D) pulse pressure (PP), as estimated using restricted cubic spline models with three knots. The unadjusted hazard ratios (HRs) are represented by the solid line and the 95% confidence interval (CI) by the shaded area. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure. Previously published in 2019 in Cardiovascular Diabetology, 18:88. Reprinted with the permission of the copyright holders.

To explore the association between urinary sodium and potassium excretion and the risk of stroke, we performed Cox proportional hazards analyses. Information concerning urinary sodium and potassium excretion was available for 115 participants who had suffered an incident stroke. The 24-h Na, 24-h K, and Na/K-ratio did not increase the risk of stroke or any of its subtypes, as shown in Table 14.

TABLE 14. 24-hour urinary sodium and potassium excretion rate as a risk factor for any stroke, ischemic stroke, lacunar infarction, and hemorrhagic stroke

	Any stroke	Ischemic stroke	Lacunar infarction	Hemorrhagic stroke
24-h Na (per mmol/l)	0.99 (0.97–1.00)	1.00 (0.99–1.00)	1.00 (0.97–1.01)	1.00 (0.99–1.00)
24-h K (per mmol/l)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Na/K-ratio	1.03 (0.91–1.16)	0.90 (0.73–1.12)	0.98 (0.78–1.24)	1.19 (1.05–1.34)

The data are presented as the hazard ratio with a 95% confidence interval. The model also included the participants' sex, waist circumference, diabetes duration, diabetic nephropathy, HbA_{1c}, LDL-cholesterol, severe diabetic retinopathy, any smoking, and antihypertensive medication. The variables shown were included in separate models. 24-h Na = 24-hour sodium excretion rate, 24-h K = 24-hour potassium excretion rate, Na/K-ratio = sodium/potassium ratio.

Restricted cubic splines of the Cox proportional hazards models were performed to explore the effect of the 24-h Na, 24-h K, and Na/K-ratio on the risk of stroke. Again, linearity was not assumed in any of the analyses, and all the models were unadjusted. The results concerning any type of stroke are shown in Figure 9A-C. No increased risk of stoke was seen in the case of any stroke, which was also true for ischemic and hemorrhagic stroke (data for ischemic and hemorrhagic stroke not shown).

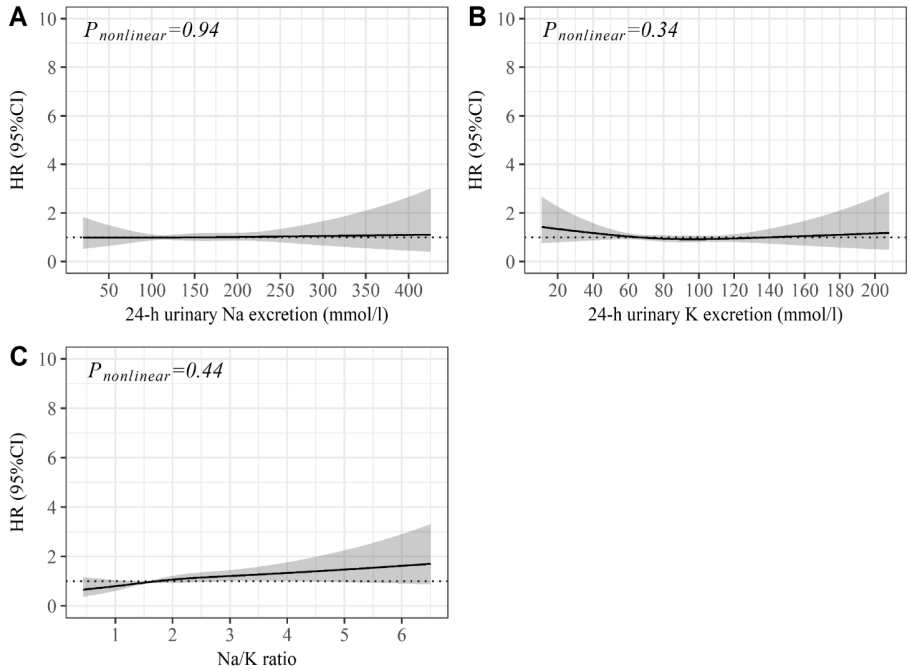

FIGURE 9. Restricted cubic spline models for any stroke and the 24-h Na, 24-h K, and Na/K ratio. The risk of any stroke in relation to (A) 24-hour urinary sodium excretion (24-h Na), (B) 24-hour urinary potassium excretion (24-h K), and (C) sodium/potassium ratio (Na/K ratio), as estimated using restricted cubic spline models with three knots. The unadjusted hazard ratios (HRs) are represented by the solid line and the 95% confidence interval (CI) by the shaded area. Previously published in 2019 in Cardiovascular Diabetology, 18:88 as additional data. Reprinted with the permission of the copyright holders.

6.4 Prognosis and predictors following an incident stroke (Study IV)

Study IV included the original 149 participants who had suffered an incident stroke. Follow-up information was missing for three of those initial 149 participants, meaning that they were excluded from the analysis. Furthermore, two participants died from unknown causes. This resulted in a total of 144 participants being included in the study, of whom 104 (72%) had a composite endpoint during the follow-up period. The characteristics of the participants with an endpoint when compared with those without an endpoint are presented in Table 15. The participants in both groups were of a similar age at the onset of diabetes and at the time of the stroke. Moreover, equal proportions of both groups were men. The distribution of hemorrhagic stroke was similar, while lacunar infarction was more common in those participants without an event. There were no differences in the participants' blood glucose levels. A majority of participants without an event had a normal UAER, while a majority of those with a composite endpoint had end-stage renal disease. Likewise, stage 1 chronic kidney disease was more common in those without an event, while stages 3 and 5 were more common in those with a composite endpoint. Severe diabetic retinopathy and coronary heart disease were equally common in both groups, and there were no differences in either the use of medication or current smoking habits.

TABLE 15. Characteristics at the time of the first stroke of the participants with no event when compared with the participants with a composite endpoint during follow-up (composite endpoint = recurrent stroke, cardiovascular hard event, or death by cardiovascular- or diabetes-related cause)

CHARACTERISTICS **n**	**No event** **40**	**Composite endpoint** **104**
Men (%)	65	66
Age at onset of diabetes (years)	16.0 (8.0–26.0)	12.0 (7.0–19.5)
Duration of diabetes (years)	34.2 ± 8.9	36.2 ± 8.2
Age at stroke (years)	51.1 ± 9.5	50.4 ± 9.0
Incident hemorrhagic stroke (%)	23	31
Incident ischemic stroke (%)	78	69
Lacunar infarction (%)	74	47*
Non-lacunar infarction (%)	26	53*
History of TIA (%)	3	4
HbA_{1c} (%)	8.8 ± 1.3	8.8 ± 1.7
HbA_{1c} (mmol/mol)	72 ± 14	72 ± 18
Renal status		
Normal UAER (%)	28	10*
Microalbuminuria (%)	25	13
Macroalbuminuria (%)	30	21
Kidney transplant (%)	15	40*
Dialysis (%)	3	16*
ESRD (%)	18	57*
eGFR (ml/min/1.73m^2)	91 (58–107)	44 (26–66)*
Creatinine (μmol/l)	88 (61–115)	141 (92–219) *
CKD (%)		
Stage 1 (eGFR ≥ 90)	51	12*
Stage 2 (eGFR 60–89)	23	22
Stage 3 (eGFR 30–59)	18	35*
Stage 4 (eGFR 15–30)	5	13
Stage 5 (eGFR < 15 or dialysis)	3	19*
SDR (%)	75	86
CHD (%)	23	29
Atrial fibrillation		
Prior (%)	5	1
At diagnosis (%)	0	2
Aspirin (%)	50	60
Warfarin (%)	5	5
Antihypertensive medication (%)	88	91
Lipid-lowering medication (%)	50	39
Current smoking (%)	23	26

The data are presented as the mean ± standard deviation, median with interquartile range, or number of cases (%). * = $p < 0.05$. TIA = transient ischemic attack, UAER = urinary albumin excretion rate, ESRD = end-stage renal disease, eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease, SDR = severe diabetic retinopathy, CHD = coronary heart disease.

Figure 10 shows the follow-up events after the first stroke in the included participants. During the follow-up period, 33 (32%) participants with a composite endpoint suffered a recurrent stroke, 33 (32%) suffered a hard cardiovascular event, and eight (8%) suffered both a recurrent stroke and a hard cardiovascular event. All but one of the 77 participants who died, died as a result of a cardiovascular- or diabetes-related cause. Of the participants who died, 18 suffered a hard cardiovascular event before death, nine suffered a recurrent stroke, and four suffered from both endpoints. The mean follow-up period was 3.4 ± 3.1 years (range 0.0–14.7 years).

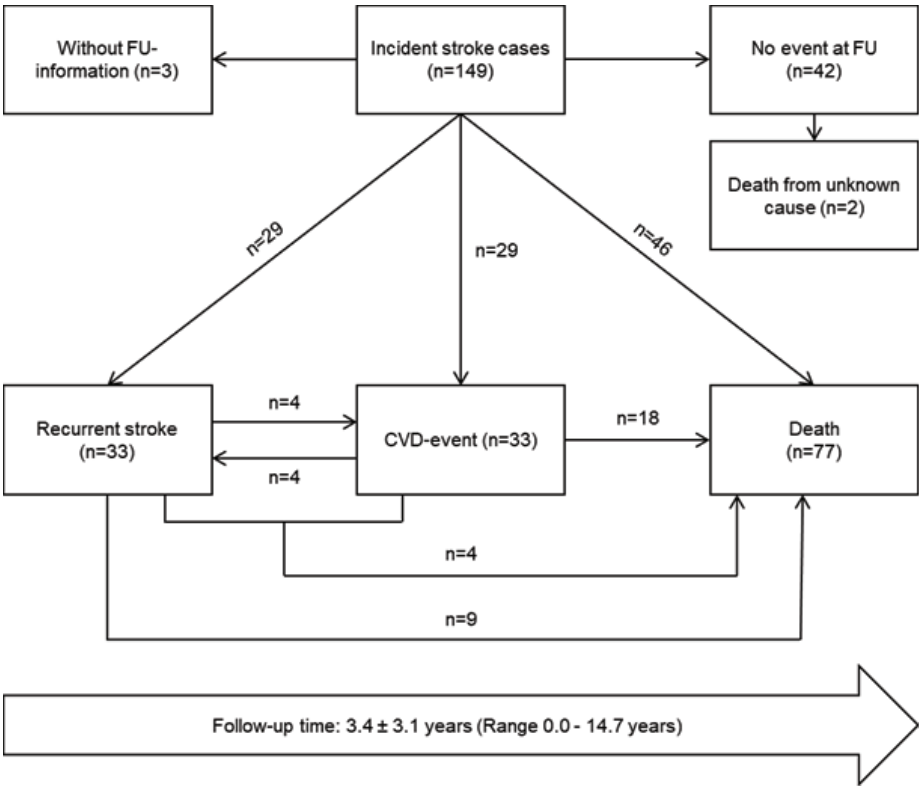

Figure 10. Flowchart of the participants who suffered an incident stroke and a composite event during the follow-up period. CVD-event = cardiovascular hard endpoint (acute myocardial infarction, coronary artery bypass surgery, or coronary angioplasty). Copyright © 2017 American Diabetes Association from Diabetes Care®, Vol.40;1394-1400. Reprinted with permission from the American Diabetes Association.

To explore survival after the initial stroke in the participants, we generated Kaplan-Meier survival plots. The results are shown in Figure 11A-C. The first plot (Figure 11A) shows the overall survival after the incident stroke. Survival was found to

decrease steadily, with the one-year survival rate being 76% and the five-year survival rate being 58%. We then stratified survival by the incident stroke type (i.e., ischemic or hemorrhagic stroke), as shown in Figure 11B. The likelihood of survival was significantly poorer if the incident stroke was of a hemorrhagic origin, with the one-year survival rate for that subtype being 52% when compared with 87% for ischemic stroke ($p < 0.001$). The difference in the survival rates decreased for five-year survival, being 46% for hemorrhagic stroke and 64% for ischemic stroke ($p = 0.038$). Since kidney function was significantly poorer in those participants with a composite endpoint, we stratified survival by the chronic kidney disease stage, as seen in Figure 11C. Survival was found to decrease significantly with deteriorating kidney function, with the one-year survival for stage 1 being 87%, for stage 2 being 88%, for stage 3 being 81%, for stage 4 being 64%, and for stage 5 being 50% ($p = 0.008$). Moreover, the five-year survival for stage 1 was 87%, for stage 2 was 63%, for stage 3 was 52%, for stage 4 was 57%, and for stage 5 was 30% ($p = 0.001$).

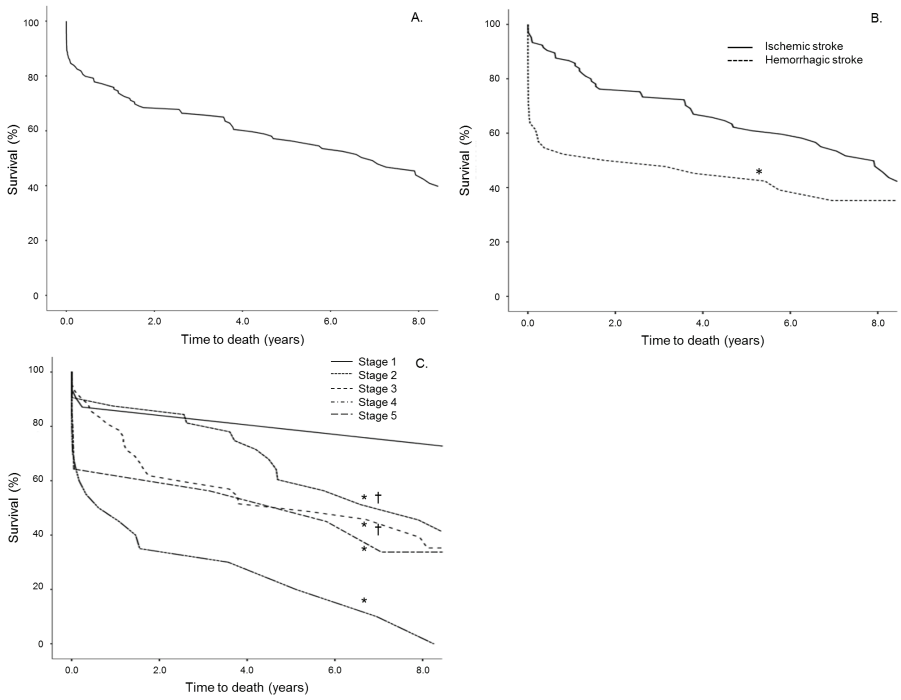

FIGURE 11. Survival after incident stroke. (A) Overall survival after incident stroke. (B) Survival stratified by incident stroke type, * = $p < 0.05$ when compared with incident ischemic stroke. (C) Survival stratified by chronic kidney disease stage, * = $p < 0.05$ when compared with stage 1, † = $p < 0.05$ when compared with stage 5. Copyright © 2017 American Diabetes Association from Diabetes Care®, Vol.40;1394-1400. Printed with permission from American Diabetes Association

In light of the results of the univariate analyses presented earlier (Table 15), we performed Cox proportional hazards analyses to determine which variables predicted a composite endpoint. The different variables of renal status and kidney function were analyzed in separate models. The results concerning the separate models are shown in Table 16. In the initial analyses, we included all the incident strokes regardless of the subtype. Model 1 included the incident stroke subtype and the renal status. The hemorrhagic stroke type, having received a kidney transplant, and being on dialysis all independently predicted a composite endpoint. Model 2 included the stroke subtype and the eGFR. Both hemorrhagic stroke and the eGFR proved to be independent predictors of the same outcome. Model 3 included the chronic kidney disease stages rather than the renal status or eGFR. In this model, the hemorrhagic stroke subtype and the chronic kidney disease stages 2–5 were all independent predictors of a composite endpoint.

TABLE 16. Predictors of a composite endpoint during follow-up after an incident stroke

	Hazard ratio for all strokes n = 4,083	**P**	**Hazard ratio for ischemic strokes n = 4,039**	**P**
Model 1				
Hemorrhagic stroke (vs. ischemic)	1.63 (1.06–2.51)	0.027	-	-
Non-lacunar infarction (vs. lacunar)	-	-	1.58 (0.99–2.54)	0.057
Renal status				
Normoalbuminuria (reference)	1.00		1.00	
Microalbuminuria	1.51 (0.66–3.46)	0.332	1.36 (0.55–3.38)	0.504
Macroalbuminuria	1.45 (0.69–3.07)	0.331	1.30 (0.58–2.90)	0.524
Kidney transplant	2.57 (1.27–5.17)	0.008	2.23 (1.03–4.80)	0.042
Dialysis	4.78 (2.16–0.60)	< 0.001	4.48 (1.78–11.2)	0.001
Model 2				P
Hemorrhagic stroke (vs. ischemic)	2.40 (1.52–3.79)	< 0.001	-	-
Non-lacunar infarction (vs. lacunar)	-	-	1.79 (1.09–2.94)	0.021
eGFR (ml/min/1.73m^2), per unit increase	0.98 (0.97–0.99)	< 0.001	0.98 (0.97–0.99)	< 0.001
Model 3				P
Hemorrhagic stroke (vs. ischemic)	2.03 (1.29–3.19)	0.002	-	-
Non-lacunar infarction (vs. lacunar)	-	-	2.00 (1.20–3.27)	0.007
CKD stage				
Stage 1 (reference)	1.00		1.00	
Stage 2	2.48 (1.17–5.24)	0.018	1.64 (0.70–3.86)	0.255
Stage 3	3.04 (1.54–6.04)	0.001	2.72 (1.21–6.12)	0.016
Stage 4	3.95 (1.72–9.04)	0.001	2.81 (0.98–8.02)	0.054
Stage 5	6.71 (3.14–14.34)	< 0.001	7.44 (2.86–19.3)	< 0.001

The data are presented as the hazard ratio with a 95% confidence interval. The variables included in the models are shown in the table under the model in question. Composite endpoint = recurrent stroke, cardiovascular hard event, or death by cardiovascular- or diabetes-related cause. eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease.

Similar analyses as performed for all the stroke types were also performed for the subtypes of ischemic stroke (i.e., lacunar or non-lacunar infarction). The results are shown in Table 16. Non-lacunar infarction was found to be an independent predictor of a composite endpoint in the model adjusted for the eGFR and chronic kidney disease, but not in the model adjusted for the renal status. The other independent predictors of a composite endpoint in these analyses were having received a kidney transplant, undergoing dialysis treatment, having a lower eGFR, and stage 3 and 5 chronic kidney disease.

We performed similar Cox regression analyses based on the univariate analyses for a recurrent stroke as the endpoint as well as for a hard cardiovascular event as the endpoint. A higher creatinine level was the only predictor we found for a recurrent stroke (HR 1.00 [1.00–1.01 per μmol/l]). A longer duration of diabetes at the time of the incident stroke (HR 1.05 [1.01–1.10]) and having received a kidney transplant (HR 5.35 [1.20–24.0]) both predicted a hard cardiovascular event. When all-cause mortality was the endpoint, the results were similar to the results concerning a recurrent stroke or a hard cardiovascular event. Furthermore, when compared with a non-lacunar infarction, having a lacunar infarction was determined to be a protective factor in relation to all-cause mortality (data not shown).

7 DISCUSSION

7.1 Strengths and weaknesses of the studies

Study population. All the participants included in Studies I to IV are part of the FinnDiane Study, which includes approximately 10% of all individuals with type 1 diabetes in Finland. Participants were recruited from all the university and central hospitals in Finland, and the geographical distribution of the FinnDiane Study centers is similar to that of the general Finnish population (see Figure 3). Thus, the cohort is considered to be a fairly good representation of all the individuals with type 1 diabetes in Finland. However, only 11% of all primary health-care centers in Finland are involved in the enrollment of participants for the FinnDiane Study. In recent years, an increasing number of individuals with type 1 diabetes who do not have any complications are being treated in primary health-care centers in Finland. Due to this, the study population might be over-representative of individuals with type 1 diabetes who are suffering from diabetic complications since such individuals are usually referred to the central and university hospitals rather than being treated in primary health-care centers. Furthermore, the recruitment of participants for the FinnDiane Study initially focused on diabetic complications, especially diabetic nephropathy.

Yet, the FinnDiane Study population has been well-studied, with the same examination protocol being followed for every participant. All the participants undergo one or more examinations, depending on whether follow-up visits have been conducted for the participant in question, by nurses and physicians at the FinnDiane Study centers. The participants' medical history, anthropometric information, and diabetic complications (if present) are recorded meticulously, and blood and urine samples are collected. The clinical data at the time of the incident stroke in Study IV were, however, not derived from centrally measured laboratory data collected during FinnDiane visits. Instead, we retrieved the data concerning the creatinine and HbA_{1c} levels at the time of the stroke from the participants' medical files. In addition, we cannot rule out the possibility that other independent predictors of survival after stroke and confounding factors exist. The same can be said for Study II, in which we could only examine those risk factors for which we had data available. Therefore, we cannot rule out the possibility that there could also have been other significant risk factors. Furthermore, no information regarding the treatment strategies after the incident stroke was available, meaning that the effect of secondary prevention could not be assessed in this study.

In terms of Study IV, only those participants with complete follow-up data were included, and all the composite endpoints were confirmed based on either medical records or death certificates. In Finland, nearly all individuals with a hard cardiovascular endpoint are treated in hospitals, and these endpoints are thoroughly documented. In the case of death outside a treatment facility, an autopsy is performed in some cases to determine the cause of death. Thus, we believe that all the events reported in this study are true events.

Classification of diabetic complications. The classification of diabetic nephropathy in this study is based on three consecutive and timed urine collections. The level of albuminuria was measured for each collection. The classification into micro- or macroalbuminuria required that the albumin excretion in two out of three collections exceeded the diagnostic concentrations presented in Table 1. Therefore, the classification of diabetic nephropathy is fairly robust. With regard to end-stage renal disease, however, no urine samples could be collected. For these participants, the classification was based on them undergoing dialysis treatment or having received a kidney transplant. A potential problem concerning the latter factor is that kidney function may improve significantly following a transplant, which might affect the risk of stroke and cardiovascular disease. This issue was not considered in Studies I to III, since the included individuals were still classified as having end-stage renal disease. In Study IV, the participants' current renal status at the time of the stroke was used, which meant that this potential bias was not apparent in that study. Another potential issue concerns the classification of severe diabetic retinopathy, which is not as exact as the classification of diabetic nephropathy. The classification of severe diabetic retinopathy in this study relied solely on laser treatment of the retina; therefore, milder forms of diabetic retinopathy and specific retinal vascular changes were not considered. Further, the classification did not consider whether the laser treatment was performed due to proliferative retinopathy or macular edema. This issue was, however, validated, as discussed in section 5.1.7. Indeed, approximately 80% of FinnDiane participants who underwent retinal laser treatment were treated for proliferative retinopathy, while the remainder were treated for maculopathy or pre-proliferative retinopathy (335).

Classification of strokes. This study investigates symptomatic strokes. One limitation with regard to the classification of strokes is that the strokes seen in individuals with type 1 diabetes are sometimes asymptomatic. Thus, we cannot exclude the possibility that those participants who were considered to be free of an incident stroke could actually have experienced a stroke without our knowledge. We are, however, fairly sure that all the participants considered to have suffered an incident stroke did indeed experience a symptomatic stroke, since all the included

strokes were identified and thoroughly classified based on the participants' medical records, brain images, or autopsy reports by experts in the field. Further, the strokes were also identified from Hilmo based on the ICD codes for stroke. Hilmo has been shown to have a positive predictive value of 75–99% when it comes to identifying common diagnoses, including stroke (342). Yet, we had to use a purely clinical definition of lacunar infarction. We could not reliably apply a more specific classification, since the participants who suffered a stroke were treated in a range of hospitals all across Finland over a period of more than 15 years. In addition, MRI data, which represent the best imaging data regarding cerebral small-vessel disease, were only available for 27% of participants.

One strength of this study concerns the considerable number of incident stroke events in a population consisting of individuals with type 1 diabetes. Despite the high incidence of stroke in those with type 1 diabetes, this cardiovascular complication is, fortunately, still a relatively rare complication in this group. The large study population enabled us to perform analyses not only of any type of stroke, but also of the stroke subtypes, especially lacunar infarction. However, another limitation is that both intracerebral and subarachnoid hemorrhages were included in the classification of hemorrhagic stroke. The causes of these two subtypes of hemorrhagic stroke may differ, as discussed in section 2.3.1. Thus, the risk factors for each subtype may also differ, which remains to be explored. Interestingly the subarachnoid hemorrhages seen in individuals with type 1 diabetes differ from those seen in the general population, with most subarachnoid hemorrhages being non-aneurysmal with a suspected microvascular cause (162). The cohort used in that study is the same as used in the studies included in the present thesis. Therefore, for the studies included in this thesis, we chose to combine ICH and SAH into a common subtype referred to as hemorrhagic stroke. Due to the limited number of hemorrhagic strokes, we could not perform analyses with regard to the independent risk factors for the two hemorrhagic stroke subtypes. The number of incident strokes, especially of the hemorrhagic subtype, might have affected the analyses of the impact of sodium and potassium on the risk of stroke as well as of the potential J-shaped association between blood pressure levels and the risk of stroke. Yet, in a prior study concerning blood pressure and its effect on the risk of stroke in those with type 2 diabetes, no J-shaped relationship between low systolic blood pressure and an increased stroke risk was found, even though the size of the study population was almost ten-fold higher than that of our study (343).

7.2 Incidence and risk of stroke in people with type 1 diabetes

The incidence of any type of stroke in individuals with type 1 diabetes was found to be 406 per 100,000 person-years (Study I). The only available information concerning the incidence of stroke among the general population in Finland explores the incidence of any type of stroke in Turku, which is just a small area of Finland. In the Turku study, the incidence of stroke was found to vary between 135 and 236 per 100,000 person-years in people aged 25–74. (344) This suggests the incidence of stroke to be almost double in individuals with type 1 diabetes in Finland. The same is seen when comparing the incidence in those with type 1 diabetes with the incidence of stroke among the general population in other high-income countries, where the incidence has been reported to be 139 per 100,000 person-years in individuals under the age of 75 (217). The age-adjusted incidence of ischemic stroke worldwide has been found to be 299 per 100,000 person-years, while for hemorrhagic stroke, the corresponding incidence has been reported to be 117 per 100,000 person-years (222). We found an incidence of 286 per 100,000 person-years for ischemic stroke and 120 per 100,000 person-years for hemorrhagic stroke (Study I). The incidence of ischemic and hemorrhagic stroke in individuals with type 1 diabetes, therefore, seem to be similar to the incidence in the general population. The study population in the present study was rather young, with a mean age of 50.5 years at the time of the stroke, which indicates these young individuals to have an incidence of stroke similar to that of people without diabetes and of a much older age. Even though the incidence of stroke was found to be higher in men, in terms of the multivariate analyses, the male sex did not appear to be a risk factor for stroke in any of the analyses (Studies I and II). This finding is congruent with the findings of other studies, where the higher risk of cardiovascular disease and stroke seen in men among the general population (22,233) was not reflected in those with type 1 diabetes (17,123). Moreover, differences in relation to sex were not seen in more recent studies concerning stroke in individuals with type 1 diabetes (345,346).

If we look closer at the incidence of stroke and its subtypes in those with type 1 diabetes, only a few studies on this subject exist. In those prior studies, the incidence of any type of stroke in individuals with type 1 diabetes was found to very between 183 per 100,000 and 475 per 100,000 person-years (13,17,347), which is largely consistent with the results of our study. To date, only one study has investigated the incidence of the subtypes of stroke in individuals with type 1 diabetes. Janghorbani *et al* studied 116,316 female registered nurses in the United States, of whom 10,766 had type 2 diabetes and 303 had type 1 diabetes. During a 24-year follow-up period, some 2,719 incident strokes were identified, and 33 participants who suffered an incident stroke had type 1 diabetes. In their study,

among the individuals with type 1 diabetes, the incidence of ischemic stroke was 288 per 100,000, while the incidence of lacunar infarction was 86 per 100,000 and the incidence of hemorrhagic stroke was 43 per 100,000 person-years. (13) The corresponding numbers in the present study are 286, 158, and 120 per 100,000 person-years, respectively (Study I). The incidence of lacunar infraction and hemorrhagic stroke were higher in our study, which can be partly explained by the age differences in the two studies. Indeed, the study population in the study by Janghorbani *et al* included only women, and they had a significantly older mean age at the time of stroke of 64 years (13) when compared with the mean age of 51 years found in the present study (Study I). Diabetic nephropathy might be more common in the participants in our study. Further, the definition of type 1 diabetes might also differ since the study by Janghorbani *et al* was a register-based study. Moreover, the different numbers of strokes included in the studies may also be responsible for the identified discrepancies. An interesting fact here is that the incidence of lacunar infarction in this study was almost double that found in the study by Janghorbani *et al.* (13) Differences in the stroke classifications applied in the two studies could explain this incongruency. However, even though stroke and its subtypes appear more commonly in individuals with type 1 diabetes, stroke is still rather rare in those individuals. This is illustrated by the fact that most studies combine stroke into a common cardiovascular endpoint because the number of strokes in the study population is so low that subanalyses concerning this cardiovascular complication prove difficult to perform.

Since the turn of the new millennium, the incidence of both cardiovascular disease and stroke in individuals with diabetes have declined worldwide (348). One explanation for this decline could be the better recognition and treatment of diabetic complications, especially diabetic nephropathy, which seems to significantly affect the risk of stroke, as seen in Studies I and II. The treatment of important risk factors in individuals with both type 1 and type 2 diabetes, such as blood glucose and blood pressure, has improved significantly over recent decades. Furthermore, the cholesterol levels seen in individuals with diabetes have also decreased. (349) Whether or not this decrease in cholesterol plays a role in the decline in the incidence of stroke in those with diabetes remains debatable. We did not find any association between cholesterol levels or triglycerides and the risk of stroke in those with type 1 diabetes in our study (Study II). As for other studies regarding cholesterol and the risk of stroke in individuals with type 1 diabetes, the Pittsburgh EDC Study found that higher non-HDL cholesterol increases the risk of stroke (17), while Rawshani *et al* showed that LDL-cholesterol, right after the systolic blood pressure and albuminuria, has one of the strongest associations with the risk of stroke in those with type 1 diabetes (346). In another study, no association between HDL-cholesterol and the stroke risk was found, while LDL-cholesterol was not considered (345). Lipid-lowering medication, however, reduced

the risk of stroke by 44% in individuals with type 1 diabetes (347). Despite the lack of relevant studies, the same inconsistencies in terms of the role of dyslipidemia in relation to the risk of stroke seen in the general population and in those with type 2 diabetes, as discussed in sections 2.3.5 and 2.3.6 (24,236,237,265), seem to be true in those with type 1 diabetes. One can only speculate about the explanations for this, although the other risk factors for stroke among the general population, and especially in those with type 1 diabetes, seem to have much stronger effects than the effect of cholesterol. Stroke is a complex disease when it comes to its pathophysiology and the development of atherosclerosis, as explained in section 2.3.1. Thus, overall, dyslipidemia appears to play a lesser role in the development of stroke. Even though no direct association between cholesterol concentrations and the risk of stroke in individuals with type 1 diabetes has been found, such individuals are at a high risk of developing cardiovascular disease. Therefore, the use of statins in individuals with type 1 diabetes should definitely be encouraged.

7.3 Effect of diabetic microvascular complications on the risk of stroke

One of the strongest risk factors for stroke, as well as for the subtypes of stroke, proved to be diabetic nephropathy (Study II). The microvascular diabetic complications were, in fact, the only factors we found that independently increased the risk of all the stroke subtypes (Study II). In other studies elucidating the independent risk factors for stroke, the presence of diabetic nephropathy, albuminuria, or lower kidney function (measured as the eGFR) were all found to be risk factors for stroke in individuals with type 1 diabetes (17,345,346). The same was seen in studies involving a common cardiovascular endpoint, with stroke being one of the endpoints (350-352). The Pittsburgh EDC Study also examined the influence of diabetic nephropathy on the subtypes of stroke and determined that overt diabetic nephropathy led to a four-fold increase in the risk of any type of stroke, as well as of ischemic stroke, while no risk was seen in relation to hemorrhagic stroke. Taking a closer look at the different stages of diabetic nephropathy was not applicable in that study. (17) When compared with the Pittsburgh EDC Study, we found a slightly lower risk of stroke and its subtypes. More specifically, we found a 2.3-fold risk of any type of stroke and a 2.8-fold risk of ischemic stroke (Study II). Yet, we also identified diabetic nephropathy to be an independent risk factor for both lacunar infarction and hemorrhagic stroke (Study II). In the analyses not adjusted for the HbA_{1c}, a new finding was that milder forms of diabetic nephropathy (presented as microalbuminuria) led to three- to four-fold increase in the risk of stroke and all its subtypes, while the highest risk was seen in relation to end-stage renal disease (a five- to 15-fold

increased risk), depending on the subtype in question (Study I). The high risk of stroke in those with end-stage renal disease has also been demonstrated in the general population, with dialysis treatment affecting the risk of stroke with a relative risk of 3.5–8.0, of ischemic stroke with a relative risk of 4.3–10.1, and of hemorrhagic stroke with a relative risk of 4.0–6.7 (353). Our results are mostly in line with these prior findings, except in relation to hemorrhagic stroke, where the risk was multifold in our study and more than 7% of participants with end-stage renal disease suffered a hemorrhagic stroke (Study I). In general, individuals on dialysis have an increased risk of cerebral hemorrhage (260) because end-stage renal disease impairs the blood platelet function (354). Further, the use of anti-coagulative medication, coupled with the presence of anemia in these individuals, enhances the bleeding tendency in those with end-stage renal disease (354), as also shown in our study.

Fortunately, the association between diabetic nephropathy and the stroke risk in individuals with type 1 diabetes does not appear to be definite. As mentioned earlier (section 2.2.1), regression from a more severe form to a milder form is possible. Regression to a lower level of albuminuria has been found to reduce the risk of cardiovascular events, including stroke, to the same level as that seen in those who did not experience progression. (68) The same risk reduction has also been identified in the general population (355) as well as in those with type 2 diabetes (356). In a similar study conducted by the DCCT/EDIC, no risk reduction in relation to cardiovascular disease was seen with regard to the remission of albuminuria. Interestingly, the regression of albuminuria did not affect the eGFR in the same way. (357) Despite the strong relationship between diabetic nephropathy and stroke, this variable represents only a crude measurement of kidney function, while the eGFR measures kidney function more precisely. When substituting diabetic nephropathy with the eGFR, a lower eGFR independently increased the risk of stroke in our study (Study II). Similarly, Wang *et al* found a linearly increasing risk of stroke with a declining eGFR in individuals with type 2 diabetes (268). In studies involving individuals with type 1 diabetes wherein diabetic nephropathy did not appear to be an independent risk factor for stroke, the GFR still appeared as an independent risk factor for stroke (345,346), suggesting that declining kidney function plays a more important role than albuminuria in the risk of stroke. In addition, not all individuals with diabetes and chronic kidney disease have albuminuria (69-71), and the risk of cardiovascular events is also increased in those with non-albuminuric chronic kidney disease when compared with those without chronic kidney disease (71).

A novel finding of our study concerns the fact that the presence of severe diabetic retinopathy, independently of diabetic nephropathy, increased the risk not only of stroke, but also of all the stroke subtypes (Study II). Surprisingly, to the best of our knowledge, this diabetic complication has not appeared as an independent

risk factor for stroke in any other studies conducted among individuals with type 1 diabetes. In those with type 2 diabetes, diabetic retinopathy has been found to increase the risk of incident stroke two-fold after adjusting for diabetic nephropathy (358). With regard to the subtypes of stroke, diabetic retinopathy increases the risk of ischemic stroke in those with type 2 diabetes if diabetic nephropathy is not considered (270). The lack of evidence concerning retinopathy as a risk factor for stroke in individuals with type 1 diabetes could partly be explained by the fact that diabetic nephropathy strongly affects the stroke risk in such individuals. Furthermore, diabetic nephropathy and diabetic retinopathy are so closely associated that the individual effects of these microvascular complications are hard to evaluate. In addition, in register-based studies, data concerning the phenotypes of diabetic retinopathy are less feasible when compared with data concerning albuminuria and kidney function. One can, however, logically assume that these two microvascular complications might well influence the risk of stroke, since the vasculature of both the retina and the kidney share the same pathophysiological features and mechanisms as the cerebral vasculature (359,360). In a large systematic review conducted by Doubal *et al*, retinopathy was clearly associated with stroke in the general population (361). Thus, the retina is considered to be a window to the cerebral vasculature, indicating that it could serve as a surrogate marker for cerebral vascular changes (362).

7.4 Risk factors for stroke and its subtypes

The independent risk factors for any stroke, ischemic stroke, and lacunar infarction were found to be quite similar, and they included a longer duration of diabetes, higher HbA_{1c}, poor glycemic control, diabetic nephropathy, severe diabetic retinopathy, higher systolic blood pressure, a history of smoking, and insulin resistance (Study II). These risk factors are consistent with the risk factors found in another study regarding stroke in individuals with type 1 diabetes (17). Since the publication of Studies I and II, other evidence has emerged. For instance, a large Swedish registry study based on register data concerning 32,611 individuals with type 1 diabetes found that a longer duration of diabetes, albuminuria, lower eGFR, higher systolic blood pressure, higher HbA_{1c}, and higher LDL-cholesterol were all independently associated with stroke (346). A study from Australia conducted by Pease *et al*, which involved cross-sectional data concerning 1,169 individuals with type 1 diabetes, showed that older age and a lower eGFR were independent risk factors for stroke (345). The risk factors identified in these new studies are in line with the risk factors found in our study (Study II).

Older age appeared to be a risk factor for stroke in individuals with type 1 diabetes in the multivariate analyses conducted in the study by Pease *et al* (345),

while both the Pittsburgh EDC Study and Rawshani *et al* found a relationship between the duration of diabetes the and stroke risk in those with type 1 diabetes (17,346). Older age is, quite naturally, one of the strongest risk factors for stroke and its subtypes in the general population (22) as well as for any type of stroke in individuals with type 2 diabetes (24,265). As discussed in section 2.2.4, the risk of cardiovascular disease arises 10–15 years earlier in individuals with type 1 diabetes when compared with the general population (123). The state of hyperglycemia seen in cases of diabetes causes similar changes to the vasculature (185-187,363) as older age causes in the general population (170,364). Further, diabetes causes premature vascular aging and accelerated atherosclerosis, which is referred to as diabetic macroangiopathy, through several other mechanisms (365). The duration of diabetes can, therefore, be considered a surrogate marker for age in individuals with type 1 diabetes, which explains the strong association between it and stroke.

Poor glycemic control (measured as elevated HbA_{1c}) was found to be an independent risk factor for any type of stroke, ischemic stroke, and lacunar infarction (Study II). This finding is in line with the findings of other studies investigating the stroke risk in individuals with type 1 diabetes (17,346). The suggestion of the role of high blood glucose levels in the development of cardiovascular disease and stroke in those with type 1 diabetes is strengthened by the risk reduction seen in relation to these complications when the intensive treatment of the blood glucose is initiated (138). The role played by hyperglycemia can be explained by the early vascular aging seen in those with type 1 diabetes (363), which we also observed in our study, where the risk of stroke and its ischemic subtypes increased with higher HbA_{1c} concentrations (Study II). The HbA_{1c} was not, however, considered to be a risk factor for ischemic stroke in the Pittsburgh EDC Study, since no differences in the HbA_{1c} concentrations were found between individuals who suffered an ischemic stroke and individuals who did not suffer a stroke. Instead, a higher white blood cell count, which is a marker of inflammation, was found to increase the risk of this subtype of stroke even though diabetic nephropathy was considered. (17) Inflammation is also a risk factor for ischemic stroke in the general population (248). We did not identify any associations between the high-sensitivity C-reactive protein and the risk of ischemic stroke (Study II), possibly due the strong influence of the diabetes duration, HbA_{1c}, diabetic microvascular complications, and systolic blood pressure on the stroke risk. Insulin resistance appeared to be an independent risk factor for any type of stroke as well as for the ischemic stroke subtypes (Study II), which is in line with findings seen in the general population (238). Moreover, Orchard *et al* found that insulin resistance increased the risk of coronary artery disease, another type of cardiovascular disease, in those with type 1 diabetes (143). We did not find any associations between stroke and the metabolic syndrome, a risk factor for stroke in both the

general population (140) and individuals with type 2 diabetes (141). The metabolic syndrome is known to be a risk factor for cardiovascular disease and stroke in those with type 1 diabetes. However, after adjusting for diabetic nephropathy in the analyses concerning stroke, this association was no longer significant. (142) This could also explain the results in our study (Study II) since the presence of diabetic nephropathy drives the risk of stroke so strongly that it overrides the effect of the metabolic syndrome.

The risk factors for hemorrhagic stroke differed somewhat from the risk factors for the other stroke subtypes, as the diabetes duration and HbA_{1c} did not affect the risk of stroke. Instead, a lower BMI increased the risk (Study II). The etiology of hemorrhagic stroke differs from that of ischemic stroke; thus, the risk factors may also be different. Additionally, as explained above, the risk factors for ICH and SAH may also differ, which should be further explored in the future. A longer diabetes duration and higher HbA_{1c} mainly affect the atherosclerotic process in the blood vessels (363,365), while hemorrhagic stroke originates from other causes (section 2.3.1). The role of the BMI in relation to the risk of hemorrhagic stroke has been demonstrated in the general population, where both a low and a very high BMI were found to be associated with an increased risk of this stroke subtype (366). In individuals with type 2 diabetes, a higher BMI has a higher protective effect against hemorrhagic stroke (367,368). The underlying mechanism behind this obesity paradox remains unknown. The FinnDiane Study has found that a lower BMI is associated with all-cause mortality in individuals with type 1 diabetes, with the presence of diabetic nephropathy partly explaining this association (369). In our study, it is possible to speculate that the high prevalence (50%) of end-stage renal disease in individuals who suffered a hemorrhagic stroke (Study I) also affected this risk. Individuals with end-stage renal disease who are undergoing dialysis treatment are often cachectic and anemic, and they are commonly treated with aspirin. This all leads to a tendency to bleed. (354) Thus, it is no surprise that these individuals have an increased risk of hemorrhagic stroke. However, neither aspirin nor warfarin treatment increased the risk of hemorrhagic stroke in our study (Study II). Another factor associated with an increased risk of hemorrhagic stroke in this study was the use of lipid-lowering medication, with an HR of 2.4 (Study II). Low LDL concentrations are known to be associated with an increased risk of ICH (264,370). The explanation for this finding is still unclear, and concerns have been raised regarding statin treatment leading to overly low LDL-cholesterol concentrations. Luckily, studies concerning statin treatment and ICH have identified only risk reductions without any adverse effect. (371)

A new finding in our study concerned the strong effect of the systolic blood pressure on the risk of stroke and all its subtypes, even after adjusting for diabetic nephropathy (Studies II and III), which contradicts the findings of the Pittsburgh EDC Study (17). More recently, Rawshani *et al* showed that the systolic blood

pressure is the most important risk factor for stroke, being even more important than diabetic nephropathy (346). When further exploring the effect of blood pressure on the risk of stroke in individuals with type 1 diabetes, we found that all the different components (i.e., systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure) independently increased this risk (Study III). The pulse pressure represents an interesting blood pressure component, since it is considered to be a marker of large arterial stiffness (133). The premature vascular aging seen in individuals with type 1 diabetes presents as a higher pulse pressure; therefore, it is no surprise that the pulse pressure is independently associated with an increased risk of stroke and the ischemic subtypes of stroke (Study III). No other studies have yet investigated the pulse pressure and stroke risk in those with type 1 diabetes; however, in studies in which stroke is pooled into a common cardiovascular endpoint, the pulse pressure has been found to independently increase the risk of cardiovascular disease (351,352). The pulse pressure, along with the systolic blood pressure, should be considered risk factors for stroke in those with type 1 diabetes as well. However, the systolic blood pressure seems to be strongest blood pressure component associated with stroke in individuals with type 1 diabetes.

The association between the blood pressure components and the risk of stroke and its subtypes proved to be linear for the systolic blood pressure and mean arterial pressure, while a non-linear trend was seen for the diastolic blood pressure and pulse pressure (Study III). The fact that the diastolic blood pressure decreases with age (280,281) and the pulse pressure represents the difference between the systolic and diastolic blood pressures explains the non-linear association we found. Rawshani *et al* found a linear relationship between the systolic blood pressure and the risk of stroke (346), while no J-shaped association similar to that found by Zhao *et al* in individuals with type 2 diabetes (29) could be seen in either Rawshani *et al´*s study or our study. Furthermore, Cederholm *et al* also found a linear association between the systolic and diastolic blood pressures and the risk of stroke in those with type 2 diabetes, while for the other assessed cardiovascular outcomes, J-shaped associations were noted (343). This could be explained by the fact that lower blood pressure levels are known to be associated with a poorer prognosis in individuals with ischemic heart disease (372), which could be explained by the presence of heart failure, renal insufficiency, or other co-morbidities that cause low blood pressure in individuals with ischemic heart disease (373). In the study conducted by Cederholm *et al*, the risk of stroke in those with type 2 diabetes started to increase at a blood pressure > 140/80 mmHg, while another study found an increased risk when the blood pressure exceeded 130/80 mmHg (374). The finding of the latter study is in line with our findings, as we noted the stroke risk to increase at a blood pressure > 130/80 mmHg (Study III). The European Society of Cardiology and the American Heart Association have

both recently published new treatment guidelines for blood pressure in individuals with diabetes. Both suggest that the treatment goal for blood pressure should be < 130/80 mmHg but not < 120/70 mmHg (375,376). Similar blood pressure targets are recommended in the newly updated Current Care Guidelines for hypertension in high-risk individuals (e.g., individuals with diabetes) in Finland (377). Our findings indicate the benefit of more stringent blood pressure control.

As a high salt intake is known to increase an individual's blood pressure (378), it could be assumed that it also increases the risk of stroke. Indeed, a higher risk of stroke has been found in individuals with a higher 24-h Na, which is a measurement of the salt intake (289,290). The same has been seen in individuals with chronic kidney disease, for whom the risk of stroke increases in a linear fashion as the 24-h Na increases (379). The majority of participants in our study had an impaired kidney function, although, no association between the 24-h Na and the risk of stroke was observed (Study III). Moreover, no protective role on the part of the 24-h K with regard to the risk of stroke, as identified in other studies (292,293), was seen in our study. The low number of participants (n = 115) with information available on their urinary sodium and potassium excretion could partly explain this difference. However, no trends toward any associations were seen in the analyses, making it unlikely that increased statistical power would have changed the results. In addition, many participants exhibited a decline in kidney function, which could affect their urinary excretion. Naturally, no urinary collections could be obtained from those participants with end-stage renal disease.

7.5 Poor survival following an incident stroke

The prognosis after an incident stroke proved to be rather poor among our study population. More than 70% of participants suffered from a cardiovascular hard event, and eventually, more than half the participants died during the relatively short mean follow-up period of 3.4 years (Study IV). The prognosis after a stroke in individuals with type 1 diabetes remains only poorly studied. To the best of our knowledge, the Pittsburgh EDC Study is the only study to have explicitly explored survival after stroke in those with type 1 diabetes. The mortality rate found in that study (87%) (17) was even higher than the rate found in our study (53%). The participants in the Pittsburgh EDC Study were younger and had a shorter duration of diabetes, meaning that the difference in mortality rates cannot be attributable to those factors. The differences could be explained by differences in the applied treatment strategies as well as by the lower number of incident strokes in the Pittsburgh EDC Study (n = 31) (17) when compared with the number in our study (n = 202). In individuals with type 2 diabetes, Eriksson *et al* found a one-year survival rate of 75% and a five-year survival rate of 50% following stroke

(329). In those with type 1 diabetes, the corresponding survival rates were found to be 76–81%, and 45–58%, respectively (17) (Study IV), which are very similar, although the age at the time of stroke in individuals was type 1 diabetes was found to be younger. In the general population, the one-year survival rate varies between 60% and 95%, while the five-year survival rate varies between 40% and 90%, mostly depending on the age of the study population. Indeed, the higher mortality rates were seen in individuals over 75 years of age, while the lower mortality rates were seen in individuals under the age of 50 (305,320). Similar mortality rates to those observed in older individuals were seen in the rather young participants (mean age of 50.4 years) in our study (Study IV). We can, therefore, conclude that death following a stroke occurs at a much earlier age in individuals with type 1 diabetes, leaving those young individuals with a far worse prognosis than the general population. Still, there is some good news, since hospitalizations and death due to cardiovascular disease and stroke in those with type 1 diabetes have decreased significantly over the past two decades (380).

In Study IV, survival was found to differ depending on the stroke subtype. More specifically, hemorrhagic stroke was associated with a worse prognosis than ischemic stroke, a finding that has also been observed in the general population (32,310,381). The influence of hemorrhagic stroke on a poor outcome is mainly illustrated by the high mortality rates associated with this stroke subtype during the first few months after the stroke. The biggest difference in the mortality rate between ischemic and hemorrhagic stroke was observed during the first few months after the incident stroke. After that point, the difference diminished, although it was still significant five years after the stroke (Study IV). Similar differences have been seen in the general population during the first few months after a stroke; however, after that, the difference in the mortality rate appears to disappear (309,310). The risk of mortality due to hemorrhagic stroke when compared with ischemic stroke is 1.4- to 1.8-fold higher among the general population (32,310,381). In our study, the HR for hemorrhagic stroke was found to be 1.6 after adjusting for diabetic nephropathy and 2.0 after adjusting for the eGFR, indicating that the risk of hemorrhagic stroke in individuals with diabetes is similar to the risk in the general population. The pathophysiology of hemorrhagic stroke differs from that of ischemic stroke, as described in section 2.3.1, causing more extensive damage to the cerebral tissue due to edema, hypoperfusion, high intracranial pressure, and possible global ischemia (182).

In the general population, an older age, the male sex, atrial fibrillation, and the presence of cardiovascular disease all predict a poor outcome (31,310,328,382), while the predictors in individuals with type 2 diabetes are an older age, atrial fibrillation, congestive heart failure, and diabetic nephropathy (34,330). Aside from hemorrhagic stroke, the only predictors that we found were all related to kidney function (i.e., diabetic nephropathy, chronic kidney disease and a lower eGFR)

(Study IV). We are not aware of any other studies concerning this subject in those with type 1 diabetes. Surprisingly, neither age nor sex differed between those with a composite endpoint and those without a composite endpoint in the univariate analyses, meaning that they were not included in the multivariate analyses. As seen in the other studies included in the present thesis, diabetic nephropathy and impaired kidney function affect the incidence and risk of stroke to a significant extent (Studies I to III). It is, therefore, no surprise that they also affect the outcome following a stroke. Chronic kidney disease and albuminuria predict both all-cause and cardiovascular mortality in individuals with type 1 diabetes, and the risk of a poor outcome increases with deteriorating kidney function (59,346,383). Depending on the definition of diabetic kidney disease applied, the risk of a poor outcome differs somewhat. In terms of diabetic nephropathy, a higher risk was only seen in those with end-stage renal disease, while in the case of chronic kidney disease, the risk had already increased at the point at which mildly decreased kidney function (an eGFR of < 90 ml/min/1.73m^2) was observed (Study IV). While albuminuria increases the risk of stroke, the post-stroke prognosis appears to be affected by kidney function rather than by the presence of albuminuria. This finding is also supported by the fact that individuals with type 1 diabetes and a normal UAER still have an excess risk of all-cause mortality (129).

Melkas *et al* found cerebral small-vessel disease to be associated with a poorer prognosis than non-lacunar infarction in the general population (319), while in a review conducted by Jackson *et al*, the opposite was found (311). In line with the study by Jackson *et al*, non-lacunar infarction was determined to be associated with a poorer prognosis in our study involving individuals with type 1 diabetes (Study IV). However, Jackson *et al* found that the difference in prognosis in relation to the subtypes of ischemic stroke was the highest immediately after the stroke, while the difference diminished in the longer term (311), which is supported by the ultra-long follow-up period of 12 years in the study by Melkas *et al* (319). As discussed earlier, cerebral small-vessel disease is more common in individuals with diabetes (20,231), a possible confounding factor, which was not considered in the studies by Melkas *et al* and Jackson *et al* (311,319). Moreover, lacunar infarctions in individuals with diabetes differ from those in the general population. Individuals with diabetes have a higher prevalence of both systemic and intracranial atherosclerosis, and the prognosis after a lacunar infarction is poorer when compared with the prognosis in the general population (384). Thus, a direct comparison between lacunar infarctions in individuals with type 1 diabetes and the general population is not feasible.

7.6 Is stroke a micro- or macrovascular complication?

It is important to consider whether stroke is a micro- or macrovascular complication in individuals with type 1 diabetes. Although the incidence and risk of lacunar infarctions are known to increase in the presence of diabetic microvascular complications, we did not find a higher proportion of lacunar infarctions in those participants with diabetic nephropathy or severe diabetic retinopathy (Studies I and II). One possible explanation for this could be that asymptomatic microvascular lesions are also common in participants with non-lacunar infarctions and cerebral hemorrhages. In a study involving individuals with type 1 diabetes without any clinical symptoms of cerebral insults, 35% of participants presented with cerebral small-vessel disease, with an especially high prevalence of cerebral microbleeds (24%) also being seen, upon MRI investigation. The prevalence of cerebral small-vessel disease was significantly higher when compared with the controls without diabetes. (232) Additionally, in individuals with type 2 diabetes, similar cerebral microvascular lesions have been found (385). Seeing that over 40% of strokes suffered by those with type 2 diabetes (20,231), and more than 60% of strokes suffered by individuals with type 1 diabetes (20), are caused by small-vessel disease, it is not logical to talk about stroke as a solely macrovascular complication in those with diabetes. The association between stroke and other diabetic microvascular complications is indisputable (Studies I and II) (17,346,350-352). In a recent review study, van Sloten *et al* presented the pathology of the development of cerebral small-vessel disease in those with type 2 diabetes, with basement membrane thickening, increased angiogenesis, increased blood-brain permeability, and altered blood flow and cerebral autoregulation all leading to perfusion defects and hypoxia (385). While similar studies involving individuals with type 1 diabetes are currently lacking, it could be assumed that the pathology is not that different. Stroke in individuals with diabetes likely has a combination of both micro- and microvascular origins, although the typical macrovascular changes, such as the stenosis of the large arteries, appear to be more uncommon in young individuals with type 1 diabetes. Further research regarding stroke as a microvascular complication in those with diabetes is needed, as the distinction between diabetic micro- and macrovascular complications is vacillating.

7.7 Future prospects

Even though the questions that informed the aims of this thesis were answered, a few other questions were raised during the study. As diabetic nephropathy proved to significantly affect the risk of stroke in individuals with type 1 diabetes, it

would be interesting to examine in further detail which risk factors are relevant in individuals with a normal UAER. In Study I, we found that the incidence of stroke in those with a normal UAER was around 120 per 100,000 person-years (section 6.1). Given that the age-adjusted incidence of stroke in the general population in Finland is 240 per 100,000 person-years (217), the rather low incidence found in our study is somewhat surprising. However, this issue concerning the bias of including "over-healthy" individuals as study participants has become evident in both the FinnDiane and DCCT/EDIC study populations. The participants who do not develop albuminuria in these study populations are, in general, better at following health directives, have a higher socioeconomic status, and are less prone to developing treatment fatigue. Thus, despite the presence of diabetes, these individuals are actually in better health than the general population (129,386). In addition, stroke is fairly rare in individuals with type 1 diabetes and a normal UAER. Taking these matters into consideration, it appears rather problematic to look closer at the stroke risk in individuals with a normal UAER, at least in our study population.

Another interesting question concerns the occurrence of cognitive disorders after an incident stroke in individuals with type 1 diabetes. As discussed in section 2.3.8, up to 30% of those who suffer a stroke in the general population later develop dementia and cognitive impairment (301). In this study, we did not take these outcomes into consideration when we investigated the prognosis after an incident stroke. Type 1 diabetes is associated with mild to moderate cognitive impairment even without the presence of stroke (387). In terms of vascular dementia and Alzheimer's disease, diabetes of any kind doubles the risk of both these dementia subtypes (388). The risk of Parkinson's disease, another neurodegenerative disorder, is also increased in individuals with type 2 diabetes, especially younger individuals with diabetic complications (389). Given that both stroke and diabetes are risk factors for dementia, one could assume that dementia of any type would appear to a greater extent in those FinnDiane participants who have suffered an incident stroke. As more extensive studies concerning neurodegenerative disorders and type 1 diabetes are still lacking, this issue would be of great interest in our study population.

Since small-vessel disease appears to be an important piece of the stroke puzzle in those with type 1 diabetes, we consider this to be a promising avenue for future research. In this study, we only had the opportunity to look more closely at lacunar infarction, an ischemic subtype of stroke. However, in the recent FinnDiane-related study by Thorn *et al*, cerebral microbleeds were found to be more common in those with type 1 diabetes than in healthy individuals without diabetes. A concerning fact in this regard is that almost 30% of individuals with type 1 diabetes experienced three or more microbleeds. (232) In the general population, a greater burden of microbleeds increases the risk of ICH (390). An objective for future research is to

more closely study the impact of these microbleeds and the risk of ICH among the FinnDiane study population. As we have seen, hemorrhagic stroke in individuals with type 1 diabetes has a devastating effect on both prognosis and survival. It is important, therefore, to develop methods capable of identifying individuals who are at a high risk of hemorrhagic stroke.

This study found that microvascular diabetic complications are closely related to the risk of stroke in individuals with type 1 diabetes. In particular, diabetic kidney disease drives this risk in all the subtypes of stroke. The traditional risk factors for stroke, such as the male sex, atrial fibrillation, and smoking, do not appear to be applicable when it comes to stroke in those with type 1 diabetes. As the prognosis following an incident stroke in individuals with type 1 diabetes is poor, greater effort in terms of preventing micro- and macrovascular complications in those with diabetes should be made. Cardiovascular disease and mortality in individuals with type 1 diabetes continue to be a great burden, not only for society, but also for the individuals in question. The findings of this study facilitate greater understanding when it comes to the prevention and treatment of this burden.

8 SUMMARY AND CONCLUSIONS

8.1 Study I

The incidence of stroke and its subtypes (i.e., ischemic stroke, lacunar infarction, and hemorrhagic stroke) are high in individuals with type 1 diabetes. The incidence of stroke and all its subtypes increase with the presence of diabetic nephropathy and severe diabetic retinopathy. Moreover, both of these diabetic complications independently increase the risk of stroke as well as ischemic stroke, lacunar infarction, and hemorrhagic stroke. There is no association between lacunar infarction and either diabetic nephropathy or severe diabetic retinopathy.

8.2 Study II

The risk factors associated with ischemic stroke and lacunar infarction differ from those associated with hemorrhagic stroke. A longer duration of diabetes, diabetic microvascular complications, poor glycemic control, higher systolic blood pressure, a history of smoking, and poor insulin sensitivity are all independently associated with an increased risk of the ischemic subtypes of stroke. The independent risk factors associated with hemorrhagic stroke also include microvascular complications and higher systolic blood pressure, in addition to a lower body mass index. The intensified treatment of both blood glucose and blood pressure in an effort to prevent the development of diabetic microvascular complications is important in relation to decreasing the risk of stroke in individuals with type 1 diabetes.

8.3 Study III

All the blood pressure components (i.e., systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure) are associated with an increased risk of stroke in individuals with type 1 diabetes. There is a linear association between both systolic blood pressure and mean arterial pressure and stroke and its subtypes, while the association between diastolic blood pressure and pulse pressure is non-linear. The risk of total stroke, ischemic stroke, and hemorrhagic stroke increases in a linear fashion at blood pressure levels lower than the current treatment goals. Urinary sodium and potassium excretion do not have an impact on the risk of stroke or any of its subtypes.

8.4 Study IV

The prognosis following an incident stroke in individuals with type 1 diabetes is poor, with only 58% of participants surviving beyond five years. These individuals have an increased risk of mortality as well as a high risk of developing cardiovascular complications. Hemorrhagic stroke is associated with a worse prognosis than ischemic stroke, especially during the first year after the incident stroke. Hemorrhagic stroke, end-stage renal disease, and chronic kidney disease (stages 2 to 5) are all independent predictors of suffering a recurrent stroke, a hard cardiovascular event, or death due to a cardiovascular or diabetes-related cause. Efforts to prevent stroke, especially diabetes-related renal changes, are important in terms of improving survival among these individuals.

8.5 General conclusions

Individuals with type 1 diabetes who suffer a stroke are generally in poorer health and have more diabetic complications, higher blood pressure, and poorer glycemic control when compared with individuals with type 1 diabetes who do not suffer a stroke. The prognosis following a stroke is also poor in the former individuals, and the presence of diabetic kidney disease substantially affects the prognosis. To prevent stroke in individuals with type 1 diabetes, the identification and treatment of the known risk factors for stroke are of the outmost importance. High-risk individuals can be identified via the regular measurement of their blood pressure and glycemic control, in addition to screening for albuminuria, reduced kidney function, and retinopathy. Through the optimal treatment of the risk factors associated with stroke, as well as through the prevention of the development of both diabetic nephropathy and diabetic retinopathy, some strokes and their devastating consequences may be prevented.

ACKNOWLEDGEMENTS

This study was conducted between 2012 and 2021 at the Folkhälsan Institute of Genetics, Folkhälsan Research Center, at the Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, as well as at the Abdominal Center, Nephrology, University of Helsinki and Helsinki University Hospital. The study was conducted under the auspices of the Doctoral Program in Clinical Research, Doctoral School in Health Sciences, Department of Medicine, University of Helsinki. I am extremely grateful to the former and present leaders of the relevant institutes, Professor Per-Henrik Groop, Professor Anna-Elina Lehesjoki, Professor Eero Honkanen, Docent Agneta Ekstrand, Professor Mikael Knip, and Professor Kirsi Pietiläinen, for providing an excellent working environment and state-of-the-art research facilities.

The FinnDiane Study was supported by the Folkhälsan Research Foundation, Wilhelm and Else Stockmann Foundation, Academy of Finland (grant numbers 316664 and 299200), Novo Nordisk Foundation (OC0013659), "Liv och Hälsa" Society, Sigrid Juselius Foundation, Päivikki and Sakari Sohlberg Foundation, Helsinki University Hospital Research Funding (TYH2018207), Medical Society of Finland, Finnish Diabetes Research Foundation, Finnish Foundation for Cardiovascular Research, European Commission, JDRF, and NIH. In addition, I am very grateful for the personal grants I received from the Medical Society of Finland, Wilhelm and Else Stockmann Foundation, the Finnish Medical Society Duodecim, "Liv och Hälsa" Society, the Biomedicum Helsinki Foundation, and the Dorothea Olivia, Karl Walter, and Jarl Walter Perklén Foundation, which made the work for this thesis possible.

I owe my deepest gratitude to my supervisors. Docent Lena Thorn is the one who introduced me to the fascinating world of diabetes. She has held my hand from the very beginning, and she has guided me through this journey with unwavering support and encouragement. I value her thoughts and help greatly, as a supervisor, as a colleague, and especially, as a friend. Professor Per-Henrik Groop's enthusiasm and wide-ranging knowledge of the field has encouraged me in my research. His advice and support have been of tremendous help over the years.

I am also very grateful for the help and support provided by Carol Forsblom, the clinical coordinator of the FinnDiane Study. Through his patience, creativeness, and inspiration, he is always able to find a solution to your problems. I value his ideas and comments deeply, and his commitment to helping me out at any hour of the day is highly appreciated.

I wish to warmly acknowledge Professor Päivi Korhonen and Docent Jussi Sipilä for the insightful advice and constructive comments they provided during their review of the manuscript. Their suggestions truly improved this thesis.

I am very thankful to have been able to participate in such a fruitful collaboration with Neurocenter, University of Helsinki and Helsinki University Hospital. Docent Jukka Putaala is gratefully acknowledged for helping with the neurological aspect of this study. Moreover, I am grateful for the kind contributions made by Ron Liebkind and Professor Turgut Tatlisumak.

I wish to thank the all the collaborators and co-authors for their valuable contributions to this work. I am very grateful for the kind help of Valma Harjutsalo and Emma Dahlström with the statistical analyses. I am also grateful to the other co-authors, Daniel Gordin, Markku Saraheimo, Nina Elonen, and Johan Wadén, for their insightful comments and contributions.

I have the privilege of being a member of the FinnDiane Study Group, and I wish to thank the whole "FinnDiane family" for providing such a great working environment. Special thanks go to Niina, Emma, Fanny, Rasmus, Jenny, Ninni, Johan, Anna Syreeni, Nadja, Stefan, Heidi, Nicu, Maija, Anna Sandelin, Jaana, Anna-Reetta, Mari, Asta, Maikki, Mira and all the other past and present FinnDiane workers for the interesting conversations, enjoyable lunchtime company, and many coffee breaks. I am also thankful for their company on the exciting conference trips, especially that to Romania and Dracula's castle. I also wish to thank Ann-Liz for introducing me to the FinnDiane Study when I was looking for a small research project during my early years in medical school.

I wish to express my gratitude to all the nurses and physicians at the various FinnDiane Study centers for recruiting the participants. I am also grateful to all the participants and their family members, who have donated their time and effort to the FinnDiane Study, thereby enabling this work.

I am so very grateful for all my family and friends, who provide me with balance in life. I owe my deepest gratitude to my dear parents, Carola and Kenneth, who have always been there for me with never-ending love and support. You have given me the courage and confidence to do my own thing in life, while always making sure I have someone to fall back on. I am thankful to Henrik's family for their support and for making me feel like part of their family. Special thanks go to my mother-in-law Anneli, who took care of my most precious ones while I was working on this thesis. I am also grateful for having the Nalleranta gang, especially Minna and Satu, who are warmly thanked for the daily serious and not-so-serious conversations, dinners, trips, and all the other fun we have had over the years. I want to thank my friends from medical school, particularly Jessica and my girls Kia, Laura, Lina, Henrika, and Ida, for their support and friendship during the years spent studying and now continuing alongside our growing families. Hanna-Mari and Timo, I am grateful that we happened to move into the same building,

an event that led to a much appreciated friendship. My colleagues and friends at Sipoo Health Care Center are also warmly acknowledged, especially my colleagues in the diabetes team. I am also very thankful for my superior Anna Peitola, who made it possible for me to work on this project whenever I needed to.

Finally, I would like to dedicate this work to my family. Lucas and Alva, my beautiful children, my most precious ones. I want to thank you both for all the hugs, kisses, laughs, and joy that you give me. Every day you remind me of what the most important things in life are. My deepest gratitude goes to Henrik, my husband and partner in life. You are my person and my rock. I want to thank you for all your love and support throughout this journey, for always believing in me, and for pushing me to do things I did not think were possible.

Espoo, February 2021

Stefanie Hägg-Holmberg

APPENDIX

The Finnish Diabetic Nephropathy Study centers	Physicians and nurses
Anjalankoski Health Center	S. Koivula, T. Uggeldahl
Central Finland Central Hospital, Jyväskylä	T. Forslund, A. Halonen, A. Koistinen, P. Koskiaho, M. Laukkanen, J. Saltevo, M. Tiihonen
Central Hospital of Åland Islands, Mariehamn	M. Forsen, H. Granlund, A.-C. Jonsson, B. Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P. Kinnunen, A. Orvola, T. Salonen, A. Vähänen
Central Hospital of Kymenlaakso, Kotka	R. Paldanius, M. Riihelä, L. Ryysy
Central Hospital of Länsi-Pohja, Kemi	H. Laukkanen, P. Nyländen, A. Sademies
Central Ostrobothnian Hospital District, Kokkola	S. Anderson, B. Asplund, U. Byskata, P. Liedes, M. Kuusela, T. Virkkala
City of Espoo Health Center:	
- Espoonlahti	A. Nikkola, E. Ritola
- Tapiola	M. Niska, H. Saarinen
- Samaria	E. Oukko-Ruponen, T. Virtanen
- Viherlaakso	A. Lyytinen
City of Helsinki Health Center:	
- Puistola	H. Kari, T. Simonen
- Suutarila	A. Kaprio, J. Kärkkäinen, B. Rantaeskola
- Töölö	P. Kääriäinen, J. Haaga, A.-L. Pietiläinen
City of Hyvinkää Health Center	S. Klemetti, T. Nyandoto, E. Rontu, S. Satuli-Autere
City of Vantaa Health Center:	
- Korso	R. Toivonen, H. Virtanen
- Länsimäki	R. Ahonen, M. Ivaska-Suomela, A. Jauhiainen
- Martinlaakso	M. Laine, T. Pellonpää, R. Puranen
- Myyrmäk	A. Airas, J. Laakso, K. Rautavaara
- Rekola	M. Erola, E. Jatkola
- Tikkurila	R. Lönnblad, A. Malm, J. Mäkelä, E. Rautamo Hentunen,
Heinola Health Center	J. Lagerstam
Helsinki University Hospital, Department of Medicine, Division of Nephrology	M. Feodoroff, D. Gordin, O. Heikkilä, K. Hietala, J. Fagerudd, M. Korolainen, L. Kyllönen, J. Kytö, S. Lindh, K. Pettersson-Fernholm, M. Rosengård-Bärlund, A. Sandelin, L. Thorn, J. Tuomikangas, T. Vesisenaho, J. Wadén
Herttoniemi Hospital, Helsinki	V. Sipilä
Hospital of Lounais-Häme, Forssa	T. Kalliomäki, J. Koskelainen, R. Nikkanen, N. Savolainen, H. Sulonen, E. Valtonen
Hyvinkää Hospital	L. Norvio, A. Hämäläinen
Iisalmi Hospital	E. Toivanen
Jokilaakso Hospital, Jämsä	A. Parta, I. Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S. Aranko, S. Ervasti, R. Kauppinen-Mäkelin, A. Kuusisto, T. Leppälä, K. Nikkilä, L. Pekkonen
Jyväskylä Health Center, Kyllö	K. Nuorva, M. Tiihonen

The Finnish Diabetic Nephropathy Study centers	Physicians and nurses
Kainuu Central Hospital, Kajaani	S. Jokelainen, K. Kananen, M. Karjalainen, P. Kemppainen, A.-M. Mankinen, A. Reponen, M. Sankari
Kerava Health Center	H. Stuckey, P. Suominen
Kirkkonummi Health Center	A. Lappalainen, M. Liimatainen, J. Santaholma
Kivelä Hospital, Helsinki	A. Aimolahti, E. Huovinen
Koskela Hospital, Helsinki	V. Ilkka, M. Lehtimäki
Kotka Health Center	E. Pälikkö-Kontinen, A. Vanhanen
Kouvola Health Center	E. Koskinen, T. Siitonen
Kuopio University Hospital	E. Huttunen, R. Ikäheimo, P. Karhapää, P. Kekäläinen, M. Laakso, T. Lakka, E. Lampainen, L. Moilanen, S. Tanskanen, L. Niskanen, U. Tuovinen, I. Vauhkonen, E. Voutilainen
Kuusamo Health Center	T. Kääriäinen, E. Isopoussu
Kuusankoski Hospital	E. Kilkki, I. Koskinen, L. Riihelä
Laakso Hospital, Helsinki	T. Meriläinen, P. Poukka, R. Savolainen, N. Uhlenius
Lahti City Hospital	A. Mäkelä, M. Tanner
Lapland Central Hospital, Rovaniemi	L. Hyvärinen, K. Lampela, S. Pöykkö, T. Rompasaari, S. Severinkangas, T. Tulokas
Lappeenranta Health Center	P. Erola, L. Härkönen, P. Linkola, T. Pekkanen, I. Pulli, E. Repo
Lohja Hospital	T. Granlund, K. Hietanen, M. Porrassalmi, M. Saari, T. Salonen, M. Tiikkainen
Länsi-Uusimaa Hospital, Tammisaari	I.-M. Jousmaa, J. Rinne
Loimaa Health Center	A. Mäkelä, P. Eloranta
Malmi Hospital, Helsinki	H. Lanki, S. Moilanen, M. Tilly-Kiesi
Mikkeli Central Hospital	A. Gynther, R. Manninen, P. Nironen, M. Salminen, T. Vänttinen
Mänttä Regional Hospital	I. Pirttiniemi, A.-M. Hänninen
North Karelian Hospital, Joensuu	U.-M. Henttula, P. Kekäläinen, M. Pietarinen, A. Rissanen, M. Voutilainen
Nurmijärvi Health Center	A. Burgos, K. Urtamo
Oulaskangas Hospital, Oulainen	E. Jokelainen, P.-L. Jylkkä, E. Kaarlela, J. Vuolaspuro
Oulu Health Center	L. Hiltunen, R. Häkkinen, S. Keinänen-Kiukaanniemi
Oulu University Hospital	R. Ikäheimo
Päijät-Häme Central Hospital	H. Haapamäki, A. Helanterä, S. Hämäläinen, V. Ilvesmäki, H. Miettinen
Palokka Health Center	P. Sopanen, L. Welling
Pieksämäki Hospital	V. Sevtsenko, M. Tamminen
Pietarsaari Hospital	M.-L. Holmbäck, B. Isomaa, L. Sarelin
Pori City Hospital	P. Ahonen, P. Merisalo, E. Muurinen, K. Sävelä
Porvoo Hospital	M. Kallio, B. Rask, S. Rämö
Raahe Hospital	A. Holma, M. Honkala, A. Tuomivaara, R. Vainionpää
Rauma Hospital	K. Laine, K. Saarinen, T. Salminen
Riihimäki Hospital	P. Aalto, E. Immonen, L. Juurinen
Salo Hospital	A. Alanko, J. Lapinleimu, P. Rautio, M. Virtanen
Satakunta Central Hospital, Pori	M. Asola, M. Juhola, P. Kunelius, M.-L. Lahdenmäki, P. Pääkkönen, M. Rautavirta

The Finnish Diabetic Nephropathy Study centers	Physicians and nurses
Savonlinna Central Hospital	T. Pulli, P. Sallinen, M. Taskinen, E. Tolvanen, T. Tuominen, H. Valtonen, A. Vartia, S.-L. Viitanen
Seinäjoki Central Hospital	O. Antila, E. Korpi-Hyövälti, T. Latvala, E. Leijala, T. Leikkari, M. Punkari N. Rantamäki, H. Vähävuori
South Karelia Central Hospital, Lappeenranta	T. Ensala, E. Hussi, R. Härkönen, U. Nyholm, J. Toivanen
Tampere Health Center	A. Vaden, P. Alarotu, E. Kujansuu, H. Kirkkopelto-Jokinen, M. Helin, S. Gummerus, L. Calonius, T. Niskanen, T. Kaitala, T. Vatanen
Tampere University Hospital	P. Hannula, I. Ala-Houhala, R. Kannisto, T. Kuningas, P. Lampinen, M. Määttä, H. Oksala, T. Oksanen, A. Putila, H. Saha, K. Salonen, H. Tauriainen, S. Tulokas
Tiirismaa Health Center, Hollola	T. Kivelä, L. Petlin, L. Savolainen
Turku Health Center	A. Artukka, I. Hämäläinen, L. Lehtinen, E. Pyysalo, H. Virtamo, M. Viinikkala, M. Vähätalo
Turku University Central Hospital	K. Breitholz, R. Eskola, K. Metsärinne, U. Pietilä, P. Saarinen, R. Tuominen, S. Äyräpää
Vaajakoski Health Center	K. Mäkinen, P. Sopanen
Valkeakoski Regional Hospital	S. Ojanen, E. Valtonen, H. Ylönen, M. Rautiainen, T. Immonen
Vammala Regional Hospital	I. Isomäki, R. Kroneld, L. Mustaniemi, M. Tapiolinna-Mäkelä
Vasa Central Hospital	S. Bergkulla, U. Hautamäki, V.-A. Myllyniemi, I. Rusk

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